# Differences in regional diastolic function between restrictive and normal right ventricular physiology in adult patients late after tetralogy of Fallot repair

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# Abstract

**Background:** Restrictive right ventricular physiology (RRVP) is a common finding in adult patients after tetralogy of Fallot (TOF) repair. Despite many attempts to relate this phenomenon to various factors, its clinical importance and the underlying myocardial pathologies are still enigmatic.

Aim: We sought to evaluate the regional diastolic right ventricular (RV) function in patients after TOF repair with and without RRVP.

**Methods:** A group of 112 consecutive patients with repaired TOF underwent transthoracic echocardiography with tissue Doppler imaging, cardiopulmonary exercise test, cardiac magnetic resonance, and laboratory test. Of them, 83 patients met the inclusion criteria. Regional deformations of the RV and interventricular septum (IVS) in patients with and without RRVP were compared.

**Results:** Tetralogy of Fallot patients demonstrated an inhomogeneous pattern of strain rate (SR) values in the atrial contraction phase (A wave) of the RV free wall compared to healthy volunteers. Patients with RRVP had significantly lower values of A wave curves of IVS segments (velocities and SR) and higher values of RV free wall SR during early filling (E wave) and atrial contraction phases compared to patients without RRVP. In multiple factor analysis RRVP was correlated with lower values of end-diastolic IVS velocities (A wave) and higher values of RV SR A waves.

**Conclusions:** Tissue Doppler imaging may show diastolic abnormalities in patients with RRVP. This group of patients demonstrated a deterioration in IVS diastolic function as measured by SR A waves. The diastolic function of RV free wall segments was better in patients with RRVP compared to patients without restriction of the RV measured by SR.

Key words: tetralogy of Fallot, restrictive right ventricular physiology, tissue Doppler echocardiography

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## **INTRODUCTION**

Restrictive right ventricular physiology (RRVP) is a common finding in adult patients after tetralogy of Fallot (TOF) repair [1, 2]. The end-diastolic forward flow (EDFF), which characterises RRVP, occurs when right ventricular (RV) end-diastolic pressure is equal to or exceeds pulmonary arterial diastolic pressure [2–4]. Cullen et al. [4] and others [5, 6] suggested that EDFF is caused by myocardial stiffness and reduced RV diastolic compliance, and that it is responsible for myocardial injury and low cardiac output and requires higher filling pressure as well as longer inotropic and volume support early after TOF repair. Researchers tried to correlate EDFF with RV size, pulmonary regurgitation (PR) volume/fraction, exercise tolerance, QRS duration, and the risk of symptomatic arrhythmia, including life-threatening ventricular arrhythmias [2, 7–11]. The majority of studies revealed no differences in diastolic parameters recorded from the tricuspid inflow (E wave, A wave, E/A ratio) between TOF patients with and without RRVP [1, 2]: however, some studies by the same authors pointed out shorter E wave deceleration time in RRVP patients [2, 4, 8]. Very few studies were focused on the regional function of the myocardium in patients after TOF repair. One of them concerned left ventricular (LV) diastolic function in children with RRVP [1]. The other described regional RV function in

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TOF patients with and without RRVP, but did not consider the influence of PR [7]. The aim of the present study was to analyse and compare regional diastolic RV myocardial function in patients with and without RRVP, considering the possible myocardial dysfunction that might result from the influence of other factors, i.e. PR or pulmonary stenosis.

## **METHODS**

The design of the study was approved by the Research Ethics Committee of our Institute. Informed consent was obtained from each of the 112 adult patients with repaired TOF and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki. We excluded patients with incomplete data sets and with clinical records collected in large time intervals (over one month). In total, 83 patients were included for further analysis. The study population was divided into two groups. Group 1 (16 patients) consisted of patients with RRVP (defined as the presence of EDFF in the main pulmonary artery detected by pulsed-wave Doppler in at least three consecutive heartbeats). Group 2 (67 patients) included patients without RRVP. The patients were admitted to the Institute for routine one-day control hospitalisation, during which they underwent the following examinations: electrocardiography (ECG), transthoracic echocardiography, blood test, cardiac magnetic resonance (CMR, in cases where it was not performed or clinically needed before), and cardiopulmonary exercise test (CPX).

## **Echocardiography**

The studies were performed according to the guidelines of the European Association of Cardiovascular Imaging [12]. Patients were examined at rest, during normal quiet respiration, in the left lateral and supine positions. The analyses were performed with a 3–4.5-MHz transducer (Vivid 7, GE Vingmed Ultrasound, Horten, Norway) with simultaneous ECG recording. All echocardiographic images were stored digitally and analysed off-line using customised research-dedicated software (Echo Pac version BT09, GE Healthcare, Milwaukee, WI, USA).

The RV dimensions were evaluated in two parts of the RV: inflow tract and outflow tract [13]. The RV function was measured by tricuspid annular plane systolic excursion (TAPSE) and by the percentage of RV fractional area change. Pulmonary artery and tricuspid flow velocities were recorded using pulsed- or continuous-wave (above the Nyquist limit) Doppler echocardiography. The severity of PR was assessed by PR index, the regurgitation jet width (PR-vena contracta) and pressure half time. RRVP was defined as the presence of late diastolic antegrade flow in the main pulmonary artery, resulting in premature opening of the pulmonary valve during atrial contraction.

Pulsed-wave colour tissue Doppler was obtained from apical four-chamber view; the image was optimised by narrowing the insonation angle. The RV endocardium and wall thickness were traced manually beneath the trabeculations. The tissue regional data were acquired for RV free wall as well as for the interventricular septum (IVS) using diastolic velocities and longitudinal diastolic strain rates (SRs). The average of three measurements was used for further statistical calculation. The tissue global data were calculated off-line as a mean value of all measurements from three segments of the analysed wall.

#### **Other tests**

All included patients underwent CMR examination (1.5T scanner, Avanto, Siemens, Erlangen, Germany) according to the guidelines [14, 15]. CPX was performed on a running track (ZAN Ergo 600, ZAN Messgeräte GmbH, Germany) to assess the exercise capacity. The investigators analysing the results of CPX and CMR were blinded to the results of the other tests. We also analysed blood samples to evaluate the levels of N-terminal pro–B-type natriuretic peptide and creatinine, as well as glomerular filtration rate (GFR), alanine aminotransferase (ALAT), and aspartate aminotransferase (ASPAT).

#### Statistical analysis

All parameters were checked for normal distribution (based on standardised skewness and standardised kurtosis) and were log-transformed if the values departed significantly from normality. The relationship between pairs of variables was evaluated by the Pearson product-moment correlation. One-way analysis of variance was applied to discriminate between the means of the parameters (Tukey HSD test at a p-value level  $\leq$  0.05) obtained in different groups of patients. Homogeneity of variance was investigated by the Levene's test. The model of multivariable correlation was used for testing the impact of different independent variables on the incidence of RV restriction. This was performed by factor analysis and was obtained from automatic statistical software. We modelled the observed variables as a linear function of the factors to obtain those factors that accounted for most of the variability. Factors with eigenvalues  $\geq 1.0$  were included in the analysis. P-values < 0.05 were considered statistically significant. Statgraphics Centurion version XV (Statgraphics Technologies, Inc., The Plains, VA, USA) software was used for the analysis.

# **RESULTS** *Patients' characteristics*

Eighty-three patients after TOF repair (57 men; 68.7%), aged 18–56 (mean 31.5  $\pm$  11.6) years, were prospectively studied. All were clinically stable, in sinus rhythm on ECG, and without pacemakers/implantable cardioverter-defibrillator/cardiac resynchronisation therapy devices or any important cardiac or noncardiac disorders. None of the patients were reoperated due to cardiac reasons. Sixteen patients were identified as

	Restrictive physiology (n = 16)	Non-restrictive physiology (n = 67)	р
Age at TOF repair [years]	$12.6 \pm 10.5$	11.7 ± 12.6	NS
Age at study inclusion [years]	30.3 ± 9.9	31.8 ± 12.0	NS
Time since TOF repair [years]	$20.9 \pm 6.1$	21.8 ± 7.1	NS
Repair with transannular patch	6 (37.5)	27 (40.3)	NS
NT-proBNP [pg/mL]	$433.0 \pm 686.9$	219.6 ± 292.4	NS
QRS duration [ms]	132.9 ± 33.7	$154.6 \pm 21.8$	0.002
BMI [kg/m <sup>2</sup> ]	23.6 ± 4.3	24.4 ± 4.1	NS
Saturation [%]	95.7 ± 2.1	96.0 ± 1.6	NS
RVEDV — CMR [mL/m <sup>2</sup> ]	$158.8 \pm 45.1$	143.2 ± 40.1	NS
RVESV — CMR [mL/m²]	88.0 ± 27.8	77.9 ± 27.9	NS
RV mass — CMR [g/m <sup>2</sup> ]	33.7 ± 10.0	28.7 ± 8.7	NS
RVEF — CMR [%]	47.4 ± 11.1	$46.5 \pm 7.7$	NS
PRV — CMR [mL]	39.9 ± 21.4	31.3 ± 26.9	NS
PRF — CMR [%]	$29.9 \pm 14.0$	23.5 ± 17.5	NS
MPG — TTE [mmHg]	25.1 ± 18.4	21.2 ± 12.6	NS
RVSP — TTE [mmHg]	44.5 ± 13.1	41.1 ± 11.0	NS
Right atrial area — TTE [cm²]	27.6 ± 11.1	$24.1 \pm 6.6$	NS
Tricuspid inflow time — TTE [ms]	$457.5 \pm 86.3$	409.2 ± 91.8	NS

 Table 1. Echocardiographic and cardiac magnetic resonance (CMR) characteristics of patients with and without restrictive right

 ventricular physiology

Continuous variables are expressed as mean  $\pm$  standard deviation and categorical variables as percentages. BMI — body mass index; MPG — maximal pulmonary gradient; NT-proBNP — N-terminal pro–B-type natriuretic peptide; NS — not significant; PRF — pulmonary regurgitation fraction; PRV — pulmonary regurgitation volume; RVEDV — right ventricular end-diastolic volume; RVEF — right ventricular ejection fraction; RVESV — right ventricular end-systolic volume; RVSP — right ventricular systolic pressure; TOF — tetralogy of Fallot; TTE — transthoracic echocardiography

meeting the echocardiographic criteria for RRVP (Group 1), whereas in 67 patients EDFF was not detected in the main pulmonary artery (Group 2). The characteristics of the patients are presented in Table 1. In both groups of patients the average RV volume was mildly increased but the RV mass assessed in CMR was preserved. Similarly, global RV ejection fraction was in the lower part of the reference range in both groups of patients. The study assumed a lack of statistical differences in parameters describing pulmonary valve insufficiency. The two groups of patients did not differ in terms of the clinical status (mean New York Heart Association functional class was 1.2 in Group 1 vs. 1.1 in Group 2; p = 0.6). Patients with RRVP had slightly decreased exercise tolerance (7.8 METS vs. 8.1 METS and 18.9 mL/min/kg VO2max vs. 20.8 mL/min/kg VO2max in Group 1 vs. Group 2, respectively); however, the differences were not significant (p = 0.5 and p = 0.2, respectively). Similarly, there was no distinction between the groups in the mean values of haemoglobin, GFR, ALAT, and ASPAT (p = 0.9, p = 0.9, p = 0.6, and p = 0.9, respectively).

## Regional RV myocardial diastolic function

In both groups of patients, the values of diastolic myocardial velocities and SR were lower than the values in healthy volunteers [16]. The reduction was more prominent for

parameters concerning RV than IVS (Table 2). The pattern of the normal base-apex gradient of myocardial velocities was preserved in both studied groups. Similarly, in Group 1 and 2 the SR profiles for early filling (E wave) increased toward the apical segments according to the normal model [16]. However, in both groups the patterns of RV SR curves for atrial contraction phase were discrepant from those in healthy volunteers.

The only significant difference between patients with and without RRVP was found for A wave profiles of IVS segments (velocities and SR). Unexpectedly, the mean values of SR for apical IVS segment and RV middle and apical segments during early filling (E wave) phase were higher (although not significantly) in Group 1 than in Group 2. A similar observation was made during atrial contraction (A wave) phase for SR values for RV basal and middle segments.

# Multiple factor analysis of RV restrictive physiology

Multiple factor analysis was conducted to establish the variables associated with the appearance of EDFF in the main pulmonary artery in patients after TOF repair. In view of the diversity of possible factors, the analysis was divided into two parts. Initially, we performed an analysis of regional myocardial Table 2. Regional diastolic myocardial function of the right ventricle and interventricular septum patients with and without restrictive right ventricular physiology

	Restrictive	Non-restrictive	p:	Normal
	physiology (n = 16)	physiology (n = 67)	group 1 vs. 2	values [16]
Tissue E wave velocity [cm/s]:				
IVS basal	-6.26	-7.18	NS	-8.82
IVS middle	-4.87	-5.35	NS	-7.70
IVS apical	-3.77	-3.49	NS	-5.80
IVS global	-4.97	-5.33	NS	-
RV basal	-7.19	-8.31	NS	-10.04
RV middle	-4.41	-5.19	NS	-8.56
RV apical	-1.52	-2.98	NS	-6.6
RV global	-4.37	-5.55	NS	_
Tissue A wave velocity [cm/s]:				
IVS basal	-3.43	-4.86	0.028	-5.01
IVS middle	-2.09	-3.34	0.009	-3.92
IVS apical	-0.84	-1.58	NS	-2.72
IVS global	-2.12	-3.25	0.003	-
RV basal	-4.26	-4.16	NS	-7.90
RV middle	-2.60	-2.56	NS	-6.97
RV apical	-1.26	-1.32	NS	-4.87
RV global	-2.71	-2.71	NS	-
Tissue E wave SR [s <sup>-1</sup> ]:				
IVS basal	1.30	1.51	NS	2.03
IVS middle	1.29	1.45	NS	1.77
IVS apical	1.82	1.74	NS	2.15
IVS global	1.47	1.57	NS	-
RV basal	1.94	1.94	NS	2.28
RV middle	2.08	1.95	NS	2.14
RV apical	2.39	2.07	NS	2.58
RV global	2.14	1.99	NS	_
Tissue A wave SR [s <sup>-1</sup> ]:				
IVS basal	0.67	0.88	NS	1.09
IVS middle	0.75	0.80	NS	0.98
IVS apical	0.63	0.93	0.049	0.96
IVS global	0.68	0.87	0.016	-
RV basal	0.77	0.68	NS	1.16
RV middle	0.69	0.62	NS	1.35
RV apical	0.47	0.53	NS	1.82
RV global	0.64	0.61	NS	-

A — atrial contraction phase; E — early diastolic phase; IVS — interventricular septum; RV — right ventricle; SR — strain rate

velocities for IVS and RV free wall. Four factors with eigenvalues  $\geq$  1.0 were extracted, and together they accounted for 81.49% of the variability in the entire data set. Plots of individual and extracted factors are shown in Figure 1.

Four factors with eigenvalues  $\geq$  1.0 were also extracted in the analysis of SR. Together they accounted for 69.90% of the variability in the entire data set. Plots of individual regional SRs and extracted factors are shown in Figure 2.



**Figure 1**. Plot of factors characterising regional velocity loadings; a — atrial contraction phase; api — apical segment; bas — basal segment; e — early diastolic phase; IVS interventricular septum; mid — middle segment; Rest\_Phys restrictive physiology of right ventricle; RV — right ventricle



Figure 2. Plot of factors characterising strain rate loadings; abbreviations — see Figure 1

## Echocardiographic reproducibility

Interobserver variability was based on 23 randomly selected patients. Intraclass correlation coefficient (ICC) was used to assess the reproducibility of the heart chamber size and conventional Doppler variables. The ICC for RV and LV dimensions was 0.64–0.84, for pulmonary flow measurements it was 0.51–0.65, for TAPSE — 0.39, and for RV systolic pressure — 0.48.

#### DISCUSSION

Restrictive physiology of the RV is a common observation after TOF repair, but its real prevalence is unknown. In some studies, EDFF in pulmonary arteries was observed in 40% to 70% of patients [1, 6, 17]. In relation to this, the rate of EDFF

reported in our study was rather low - it was only noticed in 19.3% of all patients. It may be due to the fact that in several studies the presence of RRVP was correlated with transannular patch (TAP) repair of TOF [6, 7, 18]. In studies including predominantly patients with restrictive physiology over other TOF patients, the TAP correction was more frequent (from  $\sim$  50% in all patients to 75% in RRVP patients) [1, 3, 6], while in our study the percentages of TAP repair in both groups were similar and did not exceed 40%. Low RRVP occurrence in our study may also be related to the large amount of time elapsed since TOF repair. In a study by Cullen et al. [4], in all but four of the 17 included patients antegrade diastolic pulmonary arterial flow was completely lost on the ninth day after TOF correction. Similarly, in a study by Norgard et al. [19], although the presence of early restriction was the only independent variable predictive of late restriction, restrictive physiology at follow-up was maintained only by nine of 16 patients, and the mean follow-up duration was only two years. We have studied our patients for about 20 years since TOF repair, which may be the reason for the low percentage of RRVP observed.

The pathology and myocardial mechanism of EDFF observed in some patients after TOF repair is still unclear. Earlier studies showed that EDFF is connected with elevated RV pressure that exceeds pulmonary artery pressure [19]. In these circumstances the RV works as a passive conduit between the right atrium and the pulmonary artery. Apitz et al. [3] demonstrated that RRVP patients had higher slope of end-diastolic pressure-volume relationship indicating increased diastolic stiffness. That should be reflected in the tricuspid inflow, and indeed in some studies shorter E wave deceleration time in RRVP patients was emphasised [2, 4, 7]. However, in data from van den Berg et al. [10] the filling of restrictive RV was similar to control subjects, but varied significantly from TOF patients without EDFF. That was also observed by Helbing et al. [8], who noticed that echocardiographic measurements of E wave deceleration gave similar results in RRVP patients and healthy children. In the study of van den Berg et al. [10], the dobutamine stress developed impaired RV relaxation that was not appreciated at rest in patients with EDFF. The question remains as to why stress showed the disturbances of RV inflow whereas EDFF was noticed at rest. Additionally, the current studies availing modern techniques like CMR showed that atrial filling fraction in EDFF patients is lower in aid of early filling fraction [9].

The authors of a single study broadly describing regional function of RV myocardium noted an interesting (although not significant) trend: the median peak diastolic velocity and peak diastolic SR for basal and middle RV free wall segments differed between RRVP and non-RRVP patients [6]. Our study revealed a few very interesting and new disturbances in regional myocardial function in TOF patients with and without restrictive RV. TOF patients have different configuration of RV SR A wave curves, which causes an incompatible base-apex gradient pattern as compared to healthy volunteers [16]. Patients with RRVP had significantly lower values of A wave curves of IVS segments (velocities and SR), but at the same time the values of SR for the same segments of RV during early filling (E wave) and atrial contraction (A wave) phases were higher compared to patients without EDFF in pulmonary artery (although not significantly). This observation was confirmed in multiple factor analysis, wherein RRVP was connected with lower values of A wave velocities of IVS and higher values of RV SR A waves. Thus, we discovered that the primary myocardial mechanism affects late diastolic myocardial function (especially IVS velocities) and subsequently, as a compensatory mechanism, the SR of RV free wall myocardium might be increased. Our study seems to be the first analysis of regional myocardial function in RRVP patients after TOF repair that concerns diastolic phases and both RV walls (free RV wall and IVS), which allows us to discover different pathologies of myocardial function in two myocardial walls.

The abnormalities in IVS function and ventricular interaction were described previously. Reversal septal motion and incoordination of LV relaxation was mentioned by Cullen et al. [4]. An important study on this subject was conducted by Muzzarelli et al. [20]. They concluded that excessive septal excursion is a marker of interventricular interaction and is associated with RV enlargement, global LV systolic function, reduced septal thickening, and LV fibrosis at the hinge points. Moreover, all patients with LV ejection fraction < 55%had abnormal septal excursion during diastole, not systole. This diastolic impairment of IVS function was associated with mechanical stress caused by RV volume overload [21]. Abd El Rahman et al. [22] examined LV function by tissue Doppler and strain echocardiography and observed reduced global and regional LV systolic functions, which were more pronounced in IVS. They considered that progressive paradoxical IVS motion and mechanical interventricular interaction could play more important roles in dyssynchrony than delayed electrical activation.

Despite increasing knowledge about the restrictive physiology of RV, important questions remain unanswered. We still do not know the reason behind different myocardial motion, and cannot predict the long-term consequences of that phenomenon. We believe that reliable knowledge of restrictive physiology in patients after TOF repair may change the strategy of treatment. The abundance of tissue data results in a variety of possible correlations, and the interpretation processes are difficult, thus more detailed studies are needed. The relationship between regional function of the RV and other parameters (e.g. exercise tests, symptoms) and the follow-up will be the focus of our next paper.

In the present study we used the technique of tissue Doppler imaging for analysis of regional myocardial function because we have a lot of experience with this method in different patients with congenital heart diseases [23]. Tissue Doppler imaging is less influenced by loading conditions, or annular/valvular pathology; however, its usefulness is highly dependent on the quality of the obtained images. In our research we had single unusable myocardial loops due to deficient visualisation. The image was optimised by narrowing the insonation angle, and the analysis was checked by a second researcher to minimise errors. The analysis of the collected data allowed us to observe the derangement of IVS myocardial function. It would be very interesting to know whether the pathologies in IVS function affect regional function of the LV. However, this aspect was not analysed because it was not considered in the study design or study aims.

Application of newer echocardiography techniques, such as speckle tracking and three-dimensional echocardiography, was beyond the scope of this study; however, further work including the latest diagnostic methods is planned to supplement the present investigations.

Nowadays haemodynamic measurements are no longer a part of the routine practice because of the technological progress of non-invasive examination. Nonetheless, the monitoring of the haemodynamic parameters (pressure, volume) of right heart cavities would be useful and could help reach appropriate conclusions.

Although the number of patients with RRVP was limited to 16, it was sufficient for most of the applied statistical methods.

In conclusion, we found differences in regional diastolic function of RV myocardium between patients with and without RRVP late after TOF repair. Patients with RRVP demonstrated a deterioration in IVS diastolic function as measured by SR A waves. The diastolic function of RV free wall segments was better in RRVP patients compared to patients without restriction of the RV.

#### Conflict of interest: none declared

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## WHAT IS NEW?

Restrictive right ventricular physiology (RRVP) is characterised by an end-diastolic forward flow in the main pulmonary artery resulting in premature opening of the pulmonary valve during atrial contraction. Despite a large amount of data on the clinical importance of this phenomenon, the myocardial mechanisms leading to RRVP are not clearly understood. The diastolic myocardial properties are detectable by techniques such as tissue Doppler imaging (measuring myocardial velocities) and strain rate analysis. We hypothesised that wider knowledge about regional myocardial function would allow identification of early diastolic dysfunction, implementation of proper follow-up, and perhaps earlier treatment. The findings may help to predict and maybe even reverse the adverse outcomes in tetralogy of Fallot patients with RRVP.