



# The influence of pulmonary regurgitation on regional right ventricular function in children after surgical repair of tetralogy of Fallot

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## Aims

Pulmonary regurgitation after repair of tetralogy of Fallot (TOF) results in right ventricular (RV) dysfunction with significant late morbidity and mortality. The aim was to assess the influence of pulmonary regurgitation on regional RV function.

## Methods and results

In 48 asymptomatic children (age  $11.1 \pm 3.3$  years) with repair of TOF, peak systolic strain rate (SR) and end-systolic strain ( $\epsilon$ ) were acquired using colour Doppler myocardial imaging. RV indices were quantified by magnetic resonance imaging. Echocardiography and exercise capacity was also performed. Forty complete data sets were analysed. An inverse linear relationship was demonstrated between the degree of pulmonary regurgitation and right ventricle end-systolic  $\epsilon$  ( $r = -0.53$ ,  $P < 0.01$ ) as well as a correlation with peak systolic SR ( $r = -0.35$ ,  $P < 0.01$ ). A correlation existed between peak  $\text{VO}_2$  and peak systolic SR ( $r = 0.51$ ,  $P = 0.001$ ) and end-systolic  $\epsilon$  ( $r = 0.33$ ,  $P < 0.05$ ).

## Conclusion

In asymptomatic children after repair of TOF, pulmonary regurgitation is associated with impaired regional systolic RV deformation indices. Regional strain and SR may be an early indicator of RV dysfunction in patients with post-TOF and pulmonary regurgitation.

## Keywords

Tetralogy • Pulmonary regurgitation • Regional function • Doppler

## Introduction

The detrimental effects of chronic pulmonary regurgitation in patients after repair of tetralogy of Fallot (TOF) are important causes of morbidity and late mortality.<sup>1,2</sup> Accurate assessment of right ventricular (RV) function might be important for optimal timing RV outflow re-valvulation. At present, magnetic resonance imaging (MRI) is considered the golden standard for accurate quantification of RV function.<sup>3,4</sup>

Cardiac Doppler myocardial imaging (CDMI) offers an alternative non-invasive method to quantify RV function. It does not rely on geometric assumptions and is based on the measurement of myocardial velocities caused by myocardial motion.<sup>5</sup> This technique allows detection of delicate regional myocardial

deformational abnormalities and has been validated for the assessment of regional function of the ventricles.<sup>6,7</sup> Strain ( $\epsilon$ ) corresponds to the extent of regional shortening/thickening and strain rate (SR) to the rate at which the deformation takes place. The main purpose of this study was to evaluate the influence of pulmonary regurgitation on systolic RV deformational properties in children with minimal symptoms.

## Methods

### Patients

Forty-eight children who presented for follow-up after repair of TOF were studied. Exclusion criteria were included: residual RV outflow tract obstruction, branch pulmonary artery stenoses (tricuspid regurgitation Doppler velocity  $> 2.5$  m/s to exclude RV hypertension

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combined with MRI velocities and anatomy), significant tricuspid regurgitation ( $\geq 2/4$  on echo-Doppler), echocardiographic evidence of restrictive RV function, and patients not in sinus rhythm. Mean age of the group was  $11.1 \pm 3.3$  years. The patients were studied  $9.2 \pm 2.7$  years after surgical repair, which was performed at an average age of  $1.8 \pm 1.1$  years. Right ventricle outflow tract reconstruction during surgery consisted of transannular patch ( $n = 27$ ), infundibular patch ( $n = 16$ ), transatrial infundibular resection, and pulmonary artery homograft ( $n = 1$ ). All children were in NYHA functional class I except one who was in class II.

All patients underwent a complete, standard two-dimensional, and echo-Doppler cardiac imaging study as well as a colour Doppler myocardial imaging study. On the same day, a MRI scan was performed. Data from the patients were compared with those of thirty age-matched healthy controls ( $10.0 \pm 3.0$  years). Ten of this group also had a MRI scan performed.

### Colour Doppler myocardial imaging

All studies were performed at high frame rates (120–180 frames  $s^{-1}$ ) with a 3.5 MHz transducer (Vingmed System V, General Electric®, Horton, Norway). Using an apical four-chamber view, regional myocardial velocities were recorded in the longitudinal direction from the base, the mid-segment, and the apex of the RV free wall. Special attention was paid to align the ultrasound beam parallel to the direction of wall motion. Pulse repetition frequency was adjusted to avoid aliasing. A cine-loop of three consecutive cardiac cycles was digitally stored. CDMI data were analysed offline using custom-made software (TVI®, Vingmed, General Electric®, Horten, Norway and Speqle®, software package for echocardiographic quantification, K.U.Leuven, Belgium). This methodology has been extensively described.<sup>8</sup> Velocity and SR curves were averaged over three consecutive cardiac cycles. From these averaged data, peak systolic velocities, peak systolic SR, and end-systolic  $\varepsilon$  were extracted.

### Cardiac magnetic resonance imaging

Studies were performed with a 1.5 Tesla Intera MRI system (Philips Medical Systems®, Best, the Netherlands). Standard views and protocols for RV volume and functional assessment were obtained.<sup>9</sup> Pulmonary artery anatomy was also evaluated to exclude branch pulmonary artery stenoses. Ventricular volume and flow analysis was carried out using Easy Vision (Philips Medical Systems®, Best, the Netherlands). The RV end-diastolic volume (RVEDV), RV end-systolic volume, RV stroke volume (RVSV), and RV ejection fraction (RVEF) were calculated for all subjects. From the phase contrast velocity mapping images, total pulmonary forward flow, pulmonary reverse flow, pulmonary regurgitant fraction (PRF), and net pulmonary forward flow were calculated. RVEF was then corrected (RVEF<sub>c</sub>) for regurgitation of the pulmonary and tricuspid valves as well as intracardiac shunts by dividing the net forward pulmonary flow by the RVEDV.

### Exercise testing procedure

Exercise testing was performed on a calibrated motor-driven treadmill using a standard protocol. Exercise capacity was measured by the determination of peak oxygen uptake ( $VO_2$ ). To check the validity of maximal exercise testing, peak heart rate and respiratory gas exchange ratios were also assessed at maximal exercise as recommended. The values for peak  $VO_2$  were expressed as mL/min/kg body weight or as a percentage of the normal mean value derived from a large pool of healthy children.

### Ethics and statistics

Informed consent was obtained. The study was approved by the local Medical Ethics Committee. Data are presented as mean  $\pm$  standard deviation. Comparison of groups was carried out using the two-tailed unpaired *t*-test. Multiple comparisons were performed by ANOVA with *post hoc* Duncan's test. Correlation analysis was carried out by using the Pearson correlation method. A *P*-value  $< 0.05$  was considered statistically significant. For CDMI data, inter- and intraobserver variability was calculated as mean percentage error.

### Results

Complete data sets of adequate quality for all investigations were available for 40 of the 48 children. All patients had variable degrees of pulmonary regurgitation on standard echocardiography.

### Magnetic resonance imaging parameters

Mean RVEF was considerably lower in the study group ( $P < 0.001$ ) and correlated inversely with the amount of pulmonary regurgitation ( $r = -0.42$ ,  $P < 0.01$ ) (Table 1). Both RVEDV and RVSV were significantly increased compared with normal values and showed a notable correlation with the PRF ( $r = 0.58$ ,  $P < 0.01$  for PRF–RVEDV and  $r = 0.34$ ,  $P < 0.05$  for PRF–RVSV, respectively). There was significant negative correlation between the PRF and the RVEF<sub>c</sub> ( $r = -0.87$ ,  $P < 0.001$ ).

### Regional systolic longitudinal function of the right ventricle

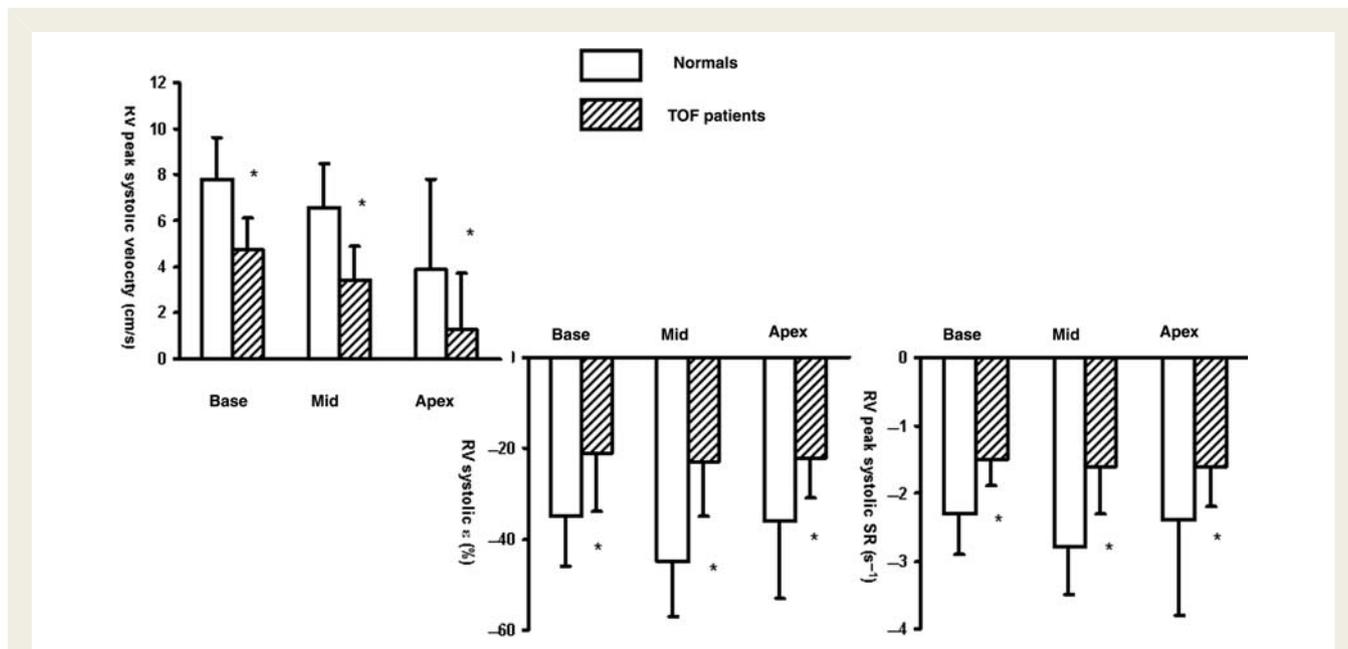
Data can be viewed in Figure 1. Peak systolic SR and end-systolic  $\varepsilon$  values were homogeneously distributed along the wall. In comparison to the normal controls, patients with a repaired TOF had reduced peak systolic velocities, as well as reduced peak systolic SR and end-systolic  $\varepsilon$  values, reflecting reduced RV longitudinal function. There was a noteworthy correlation between end-systolic  $\varepsilon$  and RVEF<sub>c</sub> ( $r = 0.38$ ,  $P < 0.01$ ). For RV end-systolic  $\varepsilon$ , the intraobserver variability was  $10.5 \pm 4.5\%$  and the interobserver variability  $11.9 \pm 5.0\%$ , and for RV peak systolic SR  $9.4 \pm 5.9\%$  and  $13.7 \pm 6.2\%$ , respectively.

An inverse linear relationship was present between the amount of pulmonary regurgitation and RV end-systolic  $\varepsilon$  ( $r = -0.53$ ,  $P < 0.01$ ) (Figure 2) and also a significant but a weaker correlation with peak systolic SR ( $r = -0.35$ ,  $P < 0.01$ ) measured at the RV base. In

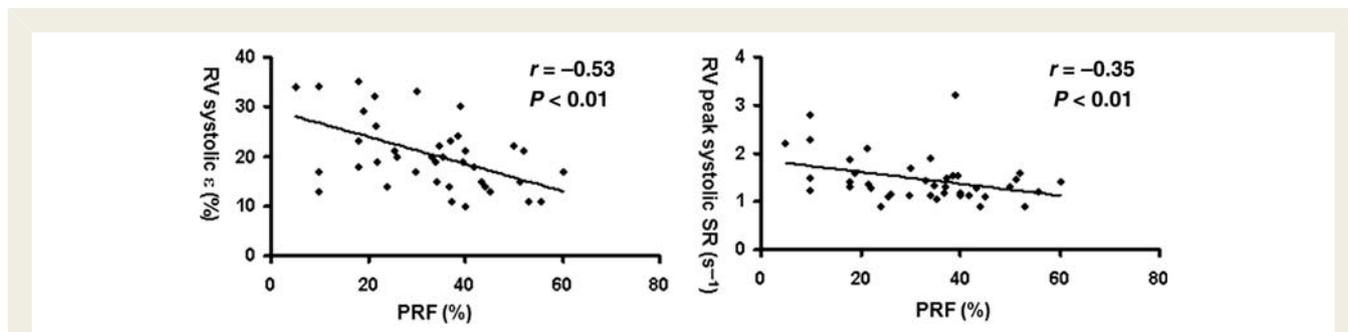
**Table 1** Magnetic resonance imaging data in patients with repaired TOF and normal subjects

	Normal ( <i>n</i> = 10)	Tetralogy of Fallot ( <i>n</i> = 40)
RVEF (%)	65.1 $\pm$ 4.0	37.3 $\pm$ 12.5 (20.1–66.3)*
RVEF <sub>c</sub> (%)	65.1 $\pm$ 4.0	56.1 $\pm$ 8.3 (39.7–73.0)*
PRF (%)	5.0 $\pm$ 2.1	32.3 $\pm$ 14.0 (5.0–60.0)*
RVEDV (mL/m <sup>2</sup> )	70.1 $\pm$ 9.2	113.2 $\pm$ 22.8 (58.1–168.9)*
RVEDV (mL/m <sup>2</sup> )	48.2 $\pm$ 7.3	62.2 $\pm$ 12.7 (35.7–83.5)*

\**P* < 0.01 TOF patients vs. normal controls.



**Figure 1** Longitudinal peak systolic velocities, peak systolic SR, and systolic  $\epsilon$  of the right ventricular free wall in patients with repaired TOF and normal controls. Note the reduction in peak systolic velocities, peak systolic SR, and systolic  $\epsilon$  in the TOF patients. In contrast, there is base-apex gradient for velocities in the TOF patients as well as in normal controls. \* $P < 0.01$  TOF patients vs. normal controls.



**Figure 2** Pearson's correlation between PRF and right ventricular deformation indices systolic  $\epsilon$  and peak systolic SR measured at the right ventricular base.

order to determine the effect of pulmonary regurgitation on regional function, CDMI data were compared for children with significant regurgitation (PRF > 30%,  $n = 22$ ) to children with mild-to-moderate regurgitation (PRF < 30%,  $n = 18$ ) as quantified by MRI. In patients with severe pulmonary regurgitation, right ventricle systolic deformation indices were significantly lower compared with those with mild-to-moderate pulmonary regurgitation (Table 2). Routine RVEF determined by MRI did not differ between the two groups. Most of the CDMI and MRI data were significantly reduced in comparison to normal controls (Table 2).

### Exercise and CDMI

Maximal exercise performance peak  $VO_2$  averaged  $39.5 \pm 5.8$  mL/min/kg or  $81.5 \pm 12.5\%$  expressed as a percent of normal. At maximal exercise, heart rate and respiratory gas exchange ratio

reached  $184 \pm 14$  bpm and  $1.04 \pm 0.06$ , respectively. There was a significant correlation between peak  $VO_2$  and RV peak systolic SR ( $r = 0.51$ ,  $P = 0.001$ ). A weaker but significant correlation could be found between peak  $VO_2$  and RV end-systolic  $\epsilon$  ( $r = 0.33$ ,  $P < 0.05$ ).

### Discussion

Pulmonary regurgitation is the predominant haemodynamic abnormality associated with sudden death and arrhythmias after the repair of TOF.<sup>10–12</sup> Pulmonary valve replacement has consistently resulted in improved outcomes.<sup>13,14</sup> Ideal selection criteria for pulmonary valve replacement is at present unclear and do not identify all those at risk for sudden death. Furthermore, it varies widely among units, since pulmonary regurgitation is

**Table 2** Comparison of magnetic resonance imaging, CDMI, and electrocardiographic data in the patients with severe vs. mild-to-moderate pulmonary regurgitation

Variable	PRF > 30% (n = 22)	PRF < 30% (n = 18)	P-value
PRF (%)	42.5 ± 7.8*	19.9 ± 8.0*	<0.0001
RVEDV (mL/m <sup>2</sup> )	123.1 ± 18.8*	99.2 ± 20.4*	0.001
RVSV (mL/m <sup>2</sup> )	66.1 ± 13.1*	58.1 ± 0.1*	0.06
RVEF (%)	53.7 ± 7.3*	58.5 ± 8.2*	0.09
RVEF <sub>c</sub> (%)	31.7 ± 5.6*	46.3 ± 9.7*	<0.0001
Peak S vel (cm/s)	4.5 ± 1.5*	4.8 ± 0.9*	0.56
Systolic $\epsilon$ (%)	-17.0 ± 4.3*	-24.6 ± 7.1*	<0.001
Peak systolic SR (s <sup>-1</sup> )	-1.29 ± 0.23*	-1.59 ± 0.45*	0.02
Heart rate (bpm)	76 ± 10	72 ± 17	0.3
QRS duration (ms)	132.9 ± 19.6*	127.4 ± 9.7*	0.28

Peak S vel, peak systolic velocity right ventricular base; systolic  $\epsilon$ , systolic strain right ventricular base; peak systolic SR, peak systolic strain rate right ventricular base; bpm, beats per minute.

\*P < 0.05 patients vs. normal controls.

generally well tolerated. However, outcome of current selection criteria is at best unknown and this chapter still needs to be written—an event that will only take place in the forthcoming two to four decades.

Impairment of RV function including regional strain and SR in patients after repair of TOF is not unique and has also been observed in other studies.<sup>9,15–17</sup> However, the majority were conducted in older patient groups and had a preponderance of adult patients. Furthermore, all subsets of patients were included, ranging from severely symptomatic, obviously needing valve replacement to asymptomatic patients. RV outflow tract obstruction was occasionally present and pulmonary regurgitation was subjectively quantified by echocardiography only.

In this study, we attempted to analyse the effects of pulmonary regurgitation as a singular factor on the right ventricle and therefore excluded patients who were significantly symptomatic as well as those with preload and afterload variables. Most importantly, pulmonary regurgitation was objectively quantified using MRI. Our results show that pulmonary regurgitation is in all probability not a benign condition. Regional systolic RV free wall function was considerably reduced in the basal, mid and apical regions in patients after repair of TOF. Of note, results for the groups based on severity of PR show that even in apparently asymptomatic children, strain and SR measurements detected significant measurable impairment of regional systolic myocardial function. Impairment of regional function became even more pronounced in patient with severe regurgitation. The inverse correlation between the PRF and  $\epsilon$  and SR indicate that regional RV systolic dysfunction reflects the effects of PR. This is consistent with other studies.<sup>18,19</sup> Routine MRI global RVEFs were not different for the two groups (53 vs. 58%) and did not identify which children already had regional RV dysfunction. RVEF<sub>c</sub> was more accurate, but the formula in effect includes PR. Combining serial CDMI measurements with those of MRI and other modalities in this select subset of patients may lead to improved decision-making in the long-term management of these children. We still do not have ideal cut-off

values for intervention, but the value of strain and SR most likely lie in serial measurements. This may assist in early identification of those at risk for complications and RV dysfunction in the decades to come. The question whether we are operating too late is still unanswered.<sup>20</sup>

The pathophysiology of impairment of regional longitudinal  $\epsilon$  and SR in the right ventricle of post-operative patients with TOF is poorly understood. Recent studies in top endurance athletes training at least 2 h per day for a minimum of 5 years demonstrated significant RV dilation and hypertrophy due to the volume load associated with exercise.<sup>21,22</sup> Arrhythmogenic properties were present in 60% of these.<sup>23</sup> Compare this to the volume loaded right ventricle of TOF with PR; continuous volume loading (24/24 h), and the clinician can expect to come across arrhythmias in the future. Pulmonary regurgitation has been shown to cause RV electro-mechanical dyssynchrony in TOF.<sup>24</sup> In addition, abnormalities of regional wall motion were detected in TOF patients with abnormalities of re- and depolarization.<sup>25</sup> We hypothesize that impaired regional function in patients with TOF reflects 'stiffness' of individual fibres, which could indicate that individual fibres are actually 'understretched' (impaired) in an overloaded ventricle because of the intrinsically abnormal myocardial substrate (different fibre architecture, fibrosis, and elastic properties).<sup>26,27</sup> This abnormal response to the chronic volume overload is highlighted in that normal regional functions were seen in patients with RV volume overload due to atrial septal defects.<sup>28</sup> Impaired regional function may thus reflect a RV on an early limb of decompensation and it is disconcerting that a recent study showed little improvement of RV regional function 6 months after valve replacement.<sup>29</sup>

A noteworthy finding is the relationship between the indices of RV deformation and the aerobic exercise performance. This study shows the burden of the pulmonary regurgitation since even children considered asymptomatic had subnormal peak VO<sub>2</sub> values. The correlation between VO<sub>2</sub> and the RV deformational indices further underlines the clinical relevance of tissue Doppler interrogation.

## Study limitations

One of the major limitations is the cross-sectional design, and the lack of longitudinal data in the present as well as other studies emphasizes the need for further studies. A limitation of using CDMI is a correct technical execution. The intra- and interobserver variability was in the region of 12% and a Bland–Altman analysis was not performed, but compares favourably to other studies using CDMI.<sup>16</sup> Speckle tracking would likely have improved accuracy, but was not locally available at the time of our study.

## Conclusion

In asymptomatic children after repair of TOF, pulmonary regurgitation is associated with impaired regional systolic RV deformation indices not demonstrated by routine RVEF. Regional strain and SR correlate with the severity of pulmonary regurgitation and may be indicative of early RV dysfunction. CDMI should be taken into account for future management of patients with post-operative TOF.

**Conflict of interest:** none declared.

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