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DOI

[10.1136/hrt.2009.175877](https://doi.org/10.1136/hrt.2009.175877)

Publication date

2009

Document Version

Final published version

Published in

Heart

[Link to publication](#)

Citation for published version (APA):

Grotenhuis, H. B., Ottenkamp, J., de Bruijn, L., Westenberg, J. J. M., Vliegen, H. W., Kroft, L. J. M., & de Roos, A. (2009). Aortic elasticity and size are associated with aortic regurgitation and left ventricular dysfunction in tetralogy of Fallot after pulmonary valve replacement. *Heart*, 95(23), 1931-1936. <https://doi.org/10.1136/hrt.2009.175877>

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Heart 2009 95: 1931-1936 originally published online August 25, 2009
doi: 10.1136/hrt.2009.175877

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Aortic elasticity and size are associated with aortic regurgitation and left ventricular dysfunction in tetralogy of Fallot after pulmonary valve replacement

H B Grotenhuis,^{1,2} J Ottenkamp,² L de Bruijn,² J J M Westenberg,¹ H W Vliegen,³ L J M Kroft,¹ A de Roos¹

¹ Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands; ² Department of Paediatric Cardiology, CAHAL: Center for Congenital Anomalies of the Heart Amsterdam/Leiden (Leiden University Medical Center, Leiden; Emma Children's Hospital/AMC, Amsterdam; VU Medical Center, Amsterdam; The Netherlands); ³ Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to:
Dr A de Roos, Leiden University Medical Center, Department of Radiology, C2-S, Albinusdreef 2, 2300 RC Leiden, The Netherlands;
A.de_Roos@lumc.nl

Accepted 4 August 2009
Published Online First
24 August 2009

ABSTRACT

Background: Aortic wall pathology and concomitant aortic dilatation have been described in tetralogy of Fallot (TOF) patients, which may negatively affect aortic valve and left ventricular systolic function.

Objective: To assess aortic dimensions, aortic elasticity, aortic valve competence and biventricular function in repaired TOF patients after pulmonary valve replacement (PVR) using magnetic resonance imaging (MRI).

Methods: MRI was performed in 16 patients with TOF after PVR (10 male; mean age 31 years (SD 15)) and 16 age and gender-matched healthy subjects.

Results: TOF patients showed aortic root dilatation (mean difference 7.8–8.8 mm, $p < 0.01$ at all four predefined levels) and reduced aortic elasticity (pulse wave velocity in aortic arch 5.5 m/s (1.2) vs 4.6 m/s (0.9), $p = 0.04$; aortic root distensibility $1.4/10^{-3}$ mm Hg (1.7) vs $5.7/10^{-3}$ mm Hg (3.6), $p < 0.01$). Minor degrees of aortic regurgitation (AR) (AR fraction 6% (8) vs 1% (1), $p < 0.01$) and reduced left ventricular ejection fraction (LVEF) were present (51% (8) vs 58% (6), $p = 0.01$), whereas right ventricular ejection fraction (RVEF) was within normal limits (47% (8) vs 52% (7), $p = 0.06$). The degree of AR fraction was associated with dilatation of the aortic root ($r = 0.39$ – 0.49 , $p < 0.05$) and reduced aortic root distensibility ($r = 0.44$, $p = 0.02$), whereas reduced LVEF was correlated with degree of AR and RVEF ($r = 0.41$, $p = 0.02$ and $r = 0.49$, $p < 0.01$, respectively).

Conclusions: Aortic root dilatation and reduced aortic elasticity are frequently present in patients with TOF, in addition to minor degrees of AR and reduced left ventricular systolic function. Aortic wall pathology in repaired TOF patients may therefore represent a separate mechanism leading to left ventricular dysfunction, as part of a multifactorial process of left ventricular dysfunction.

Aortic root dilatation frequently occurs in tetralogy of Fallot (TOF) patients, ranging in incidence between 15% and 88% depending on the definition.^{1–7} Aortic root dilatation may lead to serious complications such as aortic regurgitation (AR), aneurysm formation and even aortic dissection, necessitating aortic valve and aortic root surgery.^{3, 5, 7, 8} Therefore, meticulous non-invasive follow-up of the aorta is clinically highly desirable.^{3–5, 7, 8}

Recent reports indicate that aortic dilatation and concomitant reduced aortic elasticity may have a negative effect on aortic valve function, by the loss of central coaptation and increased stress on the aortic valve leaflets during opening and closing, respectively.^{9–16} Reduced aortic elasticity is also

associated with left ventricular dysfunction and impaired coronary blood flow.^{17, 18} Aortic wall pathology in repaired TOF patients may therefore represent a separate mechanism leading to left ventricular dysfunction, in addition to other explanations such as adverse right-to-left ventricular interaction.^{19–21}

Distensibility and pulse wave velocity (PWV) in the aorta have been shown to be markers of aortic vessel wall condition, because they are mainly due to the elastic properties of the aorta,^{17, 22, 23} for which magnetic resonance imaging (MRI) has been established as an accurate non-invasive imaging tool.^{9, 10, 24} In addition, MRI is a reliable and accurate method for the assessment of aortic dimensions, aortic valve competence and biventricular function.^{21, 25, 26}

We hypothesised that aortic root dilatation in patients after repair of TOF can be attributed to aortic wall pathology as measured by abnormal aortic distensibility and PWV, and that abnormal aortic elastic properties may negatively affect aortic valve and left ventricular systolic function. In our study we examined TOF patients after pulmonary valve replacement (PVR), to minimise the possible confounding effect of adverse right-to-left ventricular interaction due to pulmonary regurgitation (PR).^{19–21} Accordingly, the purpose of the current study was to assess prospectively aortic dimensions, aortic elasticity, aortic valve competence and biventricular systolic function in repaired TOF patients after PVR by using MRI.

METHODS

Patients

The local medical ethics committee approved the study and informed consent was obtained from all participants before enrolment in the study.

Sixteen patients with TOF and 16 age and gender-matched healthy subjects were prospectively studied with MRI at our institution. All TOF patients (10 men, six women; mean age 31 years (SD 15)) were recruited from our local congenital heart disease database. Inclusion criteria consisted of a diagnosis of TOF, previous history of PVR, willingness to comply with the study procedures and written informed consent. Exclusion criteria comprised evidence of aortic valve stenosis (aortic velocity > 2.5 m/s on echocardiography),²⁷ PR exceeding 10% (one patient), aortic coarctation and/or other forms of congenital heart disease than TOF, Marfan syndrome or a

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family history of Marfan syndrome, usage of medication such as β -blockers and general contraindications to MRI.

Age and gender-matched healthy subjects were selected from our local database of healthy individuals. Characteristics and functional status as expressed as New York Heart Association (NYHA) class of the patients and healthy subjects were obtained from the patient records (table 1).

Surgical technique

Initial repair was performed in TOF patients with a transatrial-transpulmonary approach, using cardiopulmonary bypass and moderate hypothermia. A transannular patch was used in 10 patients. Fourteen patients had previously undergone Blalock-Taussig shunt insertion and one patient had received a Potts shunt before the initial repair.

PVR in all TOF patients was performed using cryopreserved pulmonary homografts. Homografts were inserted in the orthotopic pulmonary position with maximal resection of the right ventricular (RV) outflow tract patch material.

Magnetic resonance imaging

MRI was performed with a 1.5-T system (NT 15 Gyroscan Intera; Philips Medical System, Best, The Netherlands) by one researcher (with 4 years experience in cardiac MRI). Imaging sequences were previously described.^{9 10}

Aortic root dimensions were assessed by the acquisition of double-oblique transverse images perpendicular to the aorta, at the levels of the annulus of the aortic valve, the sinus of Valsalva, the sinotubular junction (STJ) and the ascending aorta; the latter at the level of the crossing of the right pulmonary artery.^{9 10}

Aortic distensibility was measured at the level of the STJ.^{9 10} Distensibility (mm Hg^{-1}) is defined as $(A_{\text{max}} - A_{\text{min}}) / (A_{\text{min}} \times (P_{\text{max}} - P_{\text{min}}))$, with A_{max} and A_{min} the maximal and minimal lumen areas (mm^2) of the STJ and P_{max} and P_{min} the systolic and diastolic blood pressures (mm Hg).^{9 10} The minimal lumen area was obtained during the isovolumetric contraction phase (just before the beginning of the systolic upslope) and the maximal lumen area was obtained at the peak of aortic flow passing through the ascending aorta.^{9 10} Minimal and maximal lumen area MRI studies were performed after manually

positioning the acquisition planes perpendicularly to the aorta at the level of the STJ, thereby correcting for through-plane motion of the aortic root during cardiac contraction.^{9 10} Simultaneous blood pressure measurements were non-invasively obtained using a semi-automatic MRI-compatible sphygmomanometer (Invivo Research Inc, 3150, Orlando, Florida, USA).²⁸

A velocity-encoded MRI sequence was performed just distal to the aortic valve for timing of the acquisition of the cross-sectional minimal and maximal area measurements and for the determination of AR. The AR fraction was calculated with the following formula: regurgitant volume/systolic forward volume $\times 100$, where volume is measured in milliliters. A similar flow sequence was used for the assessment of PR, with a through-plane velocity encoded of up to 150 cm/s .²⁹

PWV of the aorta was measured between the ascending and proximal descending aorta, and between the proximal descending aorta and the abdominal aorta just proximal to the bifurcation.¹⁰ A transverse velocity-encoded MRI sequence was applied at the level of the pulmonary trunk to measure through-plane flow in the ascending aorta and proximal descending aorta, while a second slice was prescribed in the abdominal aorta just proximal to the bifurcation.¹⁰ PWV was calculated as $\Delta x / \Delta t$ (expressed in m/s), where Δx is the aortic path length between the measurement sites and Δt is the transit time between the arrival of the systolic wave front at these sites.¹⁰

Systolic biventricular function was assessed with a steady-state free-precession cine sequence in the short-axis plane by using breath holds. A total of 12 consecutive slices were obtained (40 phases per cardiac cycle) without slice gap.³⁰

Postprocessing

Diameter and distensibility measurements of the aortic root, as well as systolic biventricular function images were analysed with an analytical software package (MASS; Medis, Leiden, The Netherlands).³⁰ The following parameters were determined for both ventricles: end-diastolic volume, end-systolic volume, stroke volume, ejection fraction and left ventricular mass.^{9 10 30} Indexation was performed according to the Mosteller formula ($\text{BSA} = \sqrt{[\text{H} \times \text{W} / 3600]}$), where BSA is the body surface area in square meters, H is the height in centimeters and W is the weight in kilograms.^{9 30}

Flow velocity-encoded MRI data were analysed with an analytical software package (FLOW; Medis).³¹ Flow curves were obtained with this method for aortic flow and pulmonary flow during the cardiac cycle.

The manual drawing of all MRI contours and analysis of the other results was performed by one researcher (with 4 years experience in cardiac MRI), which was subsequently checked by a radiologist (with 10 years experience in cardiac MRI), who was unaware of the clinical condition of the examined TOF patients.

Statistical analysis

Statistical analysis was performed using software (SPSS for Windows, version 12.0.1). All data are presented as mean values (SD), unless stated otherwise. The two-tailed Mann-Whitney U test was used to express differences between the patient and healthy subjects. Correlation between variables was expressed with the Spearman rank correlation coefficient. Linear regression analysis was used to identify predictors of variables with backward elimination procedures. Statistical significance was indicated by a p value of less than 0.05.

Table 1 Characteristics of TOF patients and healthy subjects

Characteristics	Patients (n = 16)	Healthy subjects (n = 16)
Male/female	10/6	10/6
Age at MRI, years*	31 (15)	31 (16)
Height, cm*	172 (10)	179 (10)
Weight, kg*	70 (14)	73 (16)
Body surface area, m^2 †	1.7 (0.2)	1.9 (0.4)
Systolic blood pressure, mm Hg*	118 (14)	121 (13)
Diastolic blood pressure, mm Hg*	72 (7)	73 (12)
Cardiac frequency, beats per minute*	65 (8)	67 (9)
NYHA class I/II	15/1	16/0
Age at shunt procedure, median, years	1.2 (0.8–2.4)	
Age at initial TOF repair, median, years	2.1 (1.8–3.0)	
Age at PVR, median, years	27 (23–35)	
Interval surgery—PVR, years*	24 (4)	
Interval PVR—MRI, years*	4 (4)	

*Data are expressed as mean (SD). †According to the formula: $\sqrt{[\text{height (cm)} \times \text{weight (kg)} / 3600]}$. MRI, magnetic resonance imaging; NYHA, New York Heart Association; PVR, pulmonary valve replacement; TOF, tetralogy of Fallot.

Table 2 Results of TOF patients and healthy subjects

Parameters	Patients	Healthy subjects	p Value	Mean difference
Diameter annulus, mm	36.0 (4.6)	27.2 (3.2)	<0.01	8.8
Diameter sinus of Valsalva, mm	39.3 (5.4)	30.4 (3.1)	<0.01	8.8
Diameter of STJ, mm	35.9 (4.9)	27.7 (3.6)	<0.01	8.2
Diameter ascending aorta, mm	33.6 (5.6)	25.8 (3.8)	<0.01	7.8
Distensibility at STJ, in $10^{-3}/\text{mm Hg}$	1.4 (1.7)	5.7 (3.6)	<0.01	
PWV aortic arch, m/s	5.5 (1.2)	4.6 (0.9)	0.04	
PWV descending aorta, m/s	4.9 (1.9)	4.5 (1.1)	0.48	
Aortic regurgitation fraction, %	6 (8)	1 (1)	<0.01	
LVEF, %	51 (8)	58 (6)	0.01	
Left ventricular EDV, ml/m ² *	99 (25)	98 (29)	0.87	
Left ventricular ESV, ml/m ² *	47 (15)	41 (14)	0.28	
Left ventricular SV, ml/m ² *	53 (15)	57 (18)	0.51	
Left ventricular mass, g/m ² *	55 (16)	51 (15)	0.46	
Pulmonary regurgitation fraction, %	4 (4)	2 (2)	<0.01	
RVEF (%)	47 (8)	52 (7)	0.06	
Right ventricular EDV, ml/m ² *	117 (36)	101 (28)	0.17	
Right ventricular ESV, ml/m ² *	63 (25)	48 (13)	0.04	

Data are expressed as mean (SD). *Indexed for body surface area, according to the formula: $\sqrt{[\text{height (cm)} \times \text{weight (kg)}]/3600}$.

EDV, end-diastolic volume indexed for body surface area; ESV, end-systolic volume indexed for body surface area; LVEF, left ventricular ejection fraction; PWV, pulse wave velocity; RVEF, right ventricular ejection fraction; STJ, sinotubular junction; SV, stroke volume indexed for body surface area; TOF, tetralogy of Fallot.

RESULTS

The results of the TOF patients and healthy subjects are summarised in table 2.

Aortic dimensions and elasticity

The diameters of the aortic root at all four levels were significantly increased in TOF patients compared with healthy subjects ($p < 0.01$ for all). Dilatation was most pronounced at the level of the sinus of Valsalva, with a decrease in mean difference towards the level of the ascending aorta (fig 1 and 2). The elasticity of the proximal aorta was found to be reduced in TOF patients, as PWV in the aortic arch was significantly increased and distensibility at the level of the STJ was significantly reduced. PWV in the descending aorta was relatively normal. Dilatation at all levels of the aortic root was significantly correlated with reduced distensibility of the aortic root ($r = 0.66$ – 0.72 , $p < 0.01$ for all; fig 3).

Aortic and pulmonary valve competence

In seven of 16 TOF patients minor degrees of AR were found, with the AR fraction ranging between 5% and 12% (fig 2). In none of the healthy subjects did the AR fraction exceed 5%. Dilatation and reduced elasticity of the aortic root were associated with the degree of AR, as aortic root dilatation ($r = 0.39$ – 0.49 , $p \leq 0.04$ for all four levels) and reduced distensibility of the aortic root ($r = 0.44$, $p = 0.01$) were all correlated with degree of AR fraction (fig 3). Linear regression showed that dilatation at the levels of the STJ ($r = 0.31$, $p < 0.01$) and the annulus ($r = 0.21$, $p = 0.04$), as well as reduced distensibility at the level of the STJ ($r = 0.40$, $p = 0.02$) predicted the degree of AR. Minor degrees of PR were present in four patients, with the PR fraction ranging between 6% and 10%.

Left ventricular and right ventricular function

Systolic left ventricular function, expressed by left ventricular ejection fraction (LVEF), was found to be significantly decreased

Figure 1 Aortic dilatation. Coronal (A) and transverse (B) black-blood turbo spin-echo magnetic resonance images of the ascending aorta in a 46-year-old man with repaired tetralogy of Fallot, showing a dilated ascending aorta with a maximum diameter of 4.2 cm.

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Figure 2 Aortic insufficiency. Oblique coronal (A) and sagittal (B) gradient-echo images of the ascending aorta in the same 46-year-old man with repaired tetralogy of Fallot, showing a dilated ascending aorta and central aortic valve regurgitation.

in patients after TOF compared with healthy subjects, whereas right ventricular ejection fraction (RVEF) was within normal limits. Reduced LVEF was correlated with the degree of AR and RVEF ($r = 0.41$, $p = 0.02$, and $r = 0.49$, $p < 0.01$, respectively; fig 3), but not with aortic root distensibility ($r = 0.33$, $p = 0.06$), PWV in the aortic arch ($r = 0.08$, $p = 0.69$) and PWV in the descending aorta ($r = 0.31$, $p = 0.07$). Linear regression showed that the degree of AR predicted reduced LVEF ($r = 0.61$, $p = 0.02$). Left ventricular and right ventricular dimensions (end-diastolic volume and end-systolic volume) were within normal limits in the TOF patient group, although the right ventricular end-systolic volume of the TOF patient group was significantly larger compared with healthy subjects. The mean left ventricular mass was normal in the patient group compared with healthy subjects.

DISCUSSION

The main findings of our study are: (1) patients after TOF repair show aortic root dilatation and reduced elasticity of the proximal aorta; (2) aortic root dilatation and reduced elasticity of the proximal aorta are associated with minor degrees of AR; (3) reduced left ventricular systolic function is present in TOF patients clinically doing well after PVR, and is associated with the degree of AR and RVEF.

Aortic dimensions

Significant dilatation of the aortic root was present in our patient group with repaired TOF, being most pronounced at the levels of the annulus and the sinus of Valsalva. Increased blood flow from both ventricles to the overriding aorta before surgical repair may pose increased stress on the aortic wall, which may

Figure 3 (A–C) Values of aortic root distensibility are shown versus the diameter of the sinotubular junction, degree of aortic regurgitation and left ventricular ejection fraction (LVEF), respectively. (D–F) Values of aortic regurgitation versus diameter of the aortic annulus and LVEF, and LVEF versus right ventricular ejection fraction.

lead to aortic root dilatation.^{1 5 7 8} In addition, histological changes of the aortic media have been reported resembling those observed in Marfan syndrome.^{7 8 32} A strong correlation between histological aortic wall changes and the ascending aortic circumference suggests a causative mechanism for subsequent aortic root dilatation.⁷ Whether aortic wall pathology results from an intrinsic medial abnormality inherent to TOF itself is secondary to the antecedent volume load through the aorta before TOF repair, or perhaps a combination of the two, remains difficult to distinguish.^{1 5 7 8}

Aortic dilatation has been reported to be progressive in TOF patients with aortic dilatation, with an increase of aortic dilatation at a rate of 1.7 mm/year, in contrast to 0.03 mm/year in a control TOF patient group without aortic dilatation.¹ Of even greater concern are recent case reports of aortic dissection late after the repair of TOF in two adults whose aortic roots exceeded 6.0 cm in diameter.^{33 34} Close monitoring of aortic dimensions is therefore mandatory during follow-up, especially when a dilated ascending aorta is present, although clear guidelines for an exact timeframe of follow-up are not available.^{1 34} As MRI is already a well-accepted imaging modality for follow-up of right ventricular function in TOF patients,^{2 3 19 29} assessment of aortic and left ventricular parameters may be included in the imaging protocol. At present, there is no clear consensus on β -blocker administration for the prevention of progressive dilatation of the aortic root in repaired TOF patients such as in patients with Marfan syndrome, nor at what stage aortic root surgery should be performed.¹

Aortic elasticity

Reduced elasticity of the proximal aorta in our patient group indicated that TOF is not only associated with aortic dilatation,^{1 5 7} but also with reduced aortic elasticity. In Marfan syndrome and bicuspid aortic valve disease, increased aortic stiffness has been reported due to fragmentation of elastic wall components.²⁸ Considering the many histological similarities between these entities and TOF,⁸ aortic wall abnormalities in TOF patients may also be responsible for reduced aortic elasticity.^{1 5 7 8 32} Our patient group showed diminished elasticity of the aortic root and the aortic arch, suggesting that only the proximal part of the aorta is affected in TOF patients. In patients with Marfan syndrome, aortic stiffness has proved to be an independent predictor of progressive aortic dilatation.²⁸ Evaluation of the elastic properties of the ascending aorta in patients with TOF might therefore be used analogously to identify patients who are at risk of progressive dilatation and other aortic sequelae.

Aortic valve competence

Aortic root dilatation and decreased aortic distensibility are closely related to aortic valve function, with the potential to cause AR.^{9–11} Although fewer than half of our TOF patients exhibited mild degrees of AR, dilatation and reduced elasticity of the aortic root were associated with the degree of AR. Increased dimensions of the aortic annulus may lead to loss of coaptation of the aortic valve leaflets, which may subsequently result in varying degrees of central AR.^{4 11 13} In addition, aortic valve dynamics are related to the distensibility of the aortic root. During systole, as the aortic valve opens, the aortic root should expand simultaneously.^{13 14} Any disturbance in this synchronised process results in increased stress on the aortic valve leaflets,^{14–16} which may ultimately result in degeneration of the aortic valve leaflets and consequent AR.

Left ventricular function

Left ventricular systolic function was significantly reduced in our TOF patients. Moderate to severe left ventricular dysfunction has been reported to be a strong independent predictor of impaired clinical status and the occurrence of major adverse events in long-term survivors of TOF repair.^{2 21} Despite the fact that most of our patients were identified as NYHA functional class I, reduced LVEF in our patient group may therefore be of negative prognostic value. In this study, left ventricular systolic dysfunction was associated with the degree of AR, which may be considered as the endpoint in a sequence of events. Increased left ventricular mass may occur as a consequence of AR, to maintain normal left ventricular filling pressures.¹¹ In the case of limited AR, the increased preload will lead to a normal left ventricular volume/mass ratio with adequate preservation of LVEF.⁹ When AR progresses, the concomitant increased wall stress will result in left ventricular systolic dysfunction and reduced LVEF.¹¹

Left ventricular dysfunction in TOF patients is probably due to a multifactorial process, being explained by preoperative cyanosis, perioperative sequelae and adverse right-to-left ventricular interaction: longstanding PR in repaired TOF patients will lead to right ventricular dilatation, which is associated with increased left ventricular end-systolic volume and impaired septal contractility, having an adverse effect on left ventricular systolic performance.^{2 3 19–21} In this study, TOF patients after PVR were investigated with only minor degrees of PR, to minimise the possible confounding effect of adverse right-to-left ventricular interaction. Senzaki *et al*³² recently reported augmented aortic wave reflections and increased aortic and peripheral arterial stiffness in a group of TOF patients, which contributes to pulsatile load on the left ventricular and adversely affects left ventricular ejection. Although in this study the increased aortic stiffness was not significantly correlated with reduced left ventricular function, aortic dilatation and reduced aortic elasticity due to aortic wall pathology in repaired TOF patients may have a contributory effect on the development of AR and subsequent left ventricular dysfunction.^{19–21}

Our study has limitations. First, our study design is observational and therefore longitudinal follow-up studies are required to determine the prognostic value of our findings. No preoperative and follow-up measurements were available, so the progression of findings could not be documented. Second, relatively weak correlation coefficients between the investigated variables were found, so other contributory factors to left ventricular dysfunction may also play a role.

In conclusion, our study findings revealed frequent aortic root dilatation and reduced elasticity of the proximal aorta in patients after the repair of TOF, associated with minor degrees of AR and reduced left ventricular systolic function. Aortic wall pathology in repaired TOF patients may therefore represent a separate mechanism leading to AR and left ventricular dysfunction, as part of a multifactorial process of left ventricular dysfunction. Our study showed the feasibility of MRI as an integrated imaging tool to monitor aortic and left ventricular function parameters, which may facilitate the early detection of left ventricular dysfunction in patients after repaired TOF. Assessment of aortic and left ventricular function parameters should therefore be part of already routine MRI of right ventricular function in TOF patients.

Competing interests: None.

Ethics approval: The local medical ethics committee approved the study.

Patient consent: Obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

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