



LUND UNIVERSITY

Restrictive right ventricular physiology after Tetralogy of Fallot repair is associated with fibrosis of the right ventricular outflow tract visualized on cardiac magnetic resonance imaging.

Munkhammar, Peter; Carlsson, Marcus; Arheden, Håkan; Pesonen, Erkki

Published in:
European Heart Journal-Cardiovascular Imaging

DOI:
[10.1093/ehjci/jet009](https://doi.org/10.1093/ehjci/jet009)

2013

[Link to publication](#)

Citation for published version (APA):
Munkhammar, P., Carlsson, M., Arheden, H., & Pesonen, E. (2013). Restrictive right ventricular physiology after Tetralogy of Fallot repair is associated with fibrosis of the right ventricular outflow tract visualized on cardiac magnetic resonance imaging. *European Heart Journal-Cardiovascular Imaging*, 14(10), 978-985.
<https://doi.org/10.1093/ehjci/jet009>

Total number of authors:
4

General rights

Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

**Restrictive right ventricular physiology after tetralogy of Fallot repair is associated with
fibrosis of the right ventricular outflow tract visualized on cardiac magnetic resonance
imaging**

Peter Munkhammar, MD*

Marcus Carlsson, MD, PhD[†]

Håkan Arheden, MD, PhD[†]

Erkki Pesonen, MD, PhD*

* Dep of Pediatric Cardiology and [†] Dep of Clinical Physiology, Skåne University Hospital,
Lund University, Sweden

Running title: Restrictive physiology and fibrosis in Fallot children

Address for correspondence: Peter Munkhammar, Dep of Pediatric Cardiology, Skane

University Hospital, SE-221 85 Lund, Sweden

Email peter.munkhammar@skane.se

ABSTRACT

Aims: To determine whether restrictive physiology seen in tetralogy of Fallot (TOF) patients can be explained by fibrosis of the right ventricular (RV) outflow tract. The aetiology for restrictive RV physiology after TOF repair is not known.

Methods and Results: TOF patients (n=31, 13 girls, 10.2 years \pm 2.8) were included 9.2 \pm 2.9 years after total correction and examined with CMR and Doppler-echocardiography. Cine, flow and late gadolinium contrast enhanced (LGE) CMR were performed to quantify RV volumes, pulmonary flow and regurgitation (PR) and fibrosis. Healthy children (n=12) were investigated with CMR of pulmonary flow. Forward flow during atrial contraction above mean+2SD of healthy subjects was set as a marker of restrictive physiology. Four patients were excluded due to suboptimal LGE-CMR. Fisher's exact test was used to determine the association between restrictive physiology and fibrosis. 16 patients showed fibrosis in the RVOT on LGE-CMR and CMR showed restrictive physiology in 14 of them. In the 11 patients without fibrosis in the RVOT, 1 showed restrictive physiology. The odds ratio for RVOT fibrosis in patients with restrictive RV physiology was 70.0 (CI 5.6-882.7, p<0.001). Transannular patch repair did not differ between the groups (p=0.37). The degree of RVOT fibrosis correlated positively with PR ($r^2=0.38$, p<0.001) and RV volumes ($r^2=0.51$ for EDV and $r^2=0.47$ for ESV, p<0.001).

Conclusion: There is a strong association between restrictive RV physiology detected on CMR and fibrosis of the RVOT in children after TOF repair.

INTRODUCTION

Mid-and long-term out-come after Tetralogy of Fallot (TOF) repair are nowadays excellent and life quality among those repaired is generally good¹⁻⁴. Age at repair has gradually decreased since the early era of TOF surgery without increase in mortality or need for re-intervention⁵⁻⁶. Furthermore, surgical techniques have improved with the ability to reduce the surgical trauma of the right ventricular outflow tract (RVOT) and minimize postoperative pulmonary regurgitation (PR)⁷. In some patients the diastolic properties of the RV wall allow less compliance to diastolic filling. This RV diastolic dysfunction after TOF repair has been named restrictive RV physiology and is reflected by the occurrence of an end-diastolic forward flow in the pulmonary artery (PA) detected by Doppler echocardiography⁸. Restrictive RV physiology in the setting of significant PR has been shown to be of positive prognostic value at mid term follow-up⁹ but the pathophysiological explanation to restrictive physiology is so far unknown.

Cardiac magnetic resonance imaging (CMR) permits three dimensional visualization of the RV throughout the cardiac cycle enabling functional assessment with high accuracy. Furthermore, phase velocity encoded CMR enables flow quantification of the PR with less observer dependency compared to Doppler echocardiography and CMR can also be used to detect restrictive physiology¹⁰⁻¹². Thus, CMR has become a valuable tool in the assessment of patients operated for TOF¹³⁻¹⁴. Late gadolinium contrast enhancement (LGE) CMR has been used to localize and quantify myocardial infarction and this technique has in recent years been shown to be able to visualize fibrosis of the RV in patients with congenital heart disease (CHD)¹⁵⁻¹⁸. However, no prospective study has used LGE-CMR in children with TOF to investigate the link to restrictive physiology.

Therefore, the aim of this study was to determine if restrictive physiology seen in children after TOF repair can be associated with fibrosis of the RVOT. Furthermore, we

aimed to investigate if there are differences in RV size and function in patients with fibrosis in the RVOT compared to patients without RVOT fibrosis at mid-term follow up.

METHODS

Subjects:

Patients who had undergone TOF repair, with measurable PR at Doppler echocardiography were included. Patients with residual pulmonary stenosis pressure gradient >25 mmHg on Doppler echocardiography, associated atrioventricular septum defect, double outlet right ventricle of Fallot type, pulmonary atresia with ventricular septum defect (VSD) or TOF with absent pulmonary valve were excluded as well as patients who had undergone pulmonary valve replacement (PVR). Thirty-one patients (13 girls, mean age at investigation 10.2 ± 2.8 (range 3-16) years, were prospectively included at 9.2 ± 2.9 (range 2-16) years after surgical correction. Medium age at repair was 9.5 ± 8.6 months (range 3 weeks to 1 year and 11 months). The study groups included patients surgically corrected < 6 months of age ($n=11$) and > 6 months of age ($n=20$).

The local institutional ethics committee approved the study, and parents gave informed consent to the children's participation in the study. CMR and echocardiography examinations were performed within 2 days.

Echocardiography:

Transthoracic echocardiography was performed by one observer (PM) using a GE Vingmed Vivid Five system with FPA 3.5, 5 and 10 MHz transducers. Echocardiographic measurements of restrictive RV physiology were performed as previously described¹⁹. In short, restrictive RV physiology was defined as forward pulmonary flow in late diastole present throughout the respiratory cycle (Figure 1).

CMR

The CMR protocol and parameters are listed in the Appendix. CMR was performed on a 1.5 T Philips Intera CV (n= 27) and a 1.5 T Siemens Magnetom Vision (n=4). Cine, pulmonary flow velocity mapping and LGE CMR were acquired. Cine images were acquired in the RVOT plane, oblique transverse plane and/or the left ventricular short axis plane in order to determine the RV end-diastolic volume (EDV) and end-systolic volume (ESV) as well as the RV ejection fraction (EF). Flow velocity mapping CMR was performed during free breathing perpendicular to the plane of the flow in the pulmonary artery to determine the regurgitant volume and regurgitant fraction (RF).

Restrictive physiology using CMR

Forward flow during atrial contraction was used to detect restrictive physiology. In normal subjects there is slight forward flow during late diastole in flow quantification using CMR, caused by the movement of the pulmonary valve during atrioventricular displacement²⁰. Therefore, forward flow as a percentage of net forward flow during the cardiac cycle (Figure 1) was calculated in 12 healthy children (15±3 years) with normal CMR referred for screening of arrhythmogenic right-ventricular cardiomyopathy because of family history of this disease. A threshold of mean + 2 SD of the percentage forward flow during atrial contraction in healthy subjects was set as normal and values above this as restrictive physiology. Percentage forward flow in TOF-patients was defined as a forward flow in the PA during atrial contraction divided by the net (effective) flow (forward minus backward flow) (Figure 1). In a separate analysis, patients were classified as restrictive and non-restrictive physiology using visual assessment where any peak of forward flow prior to the systolic forward flow in the PA was considered as restrictive physiology^{10, 12}.

LGE-CMR was obtained for fibrosis visualization in the same plane as for cine CMR. Images were acquired 10-20 minutes after intravenous administration of Gadolinium (Gd)-based contrast agent (Gd-DOTA or Gd-DTPA, 0.2 mmol/kg body weight).

Image analysis

Echocardiography images were analysed without knowledge of CMR findings and vice versa.

The echocardiography images were evaluated by vendor provided software in the scanner.

CMR data were analysed using the software Segment v1.8 (<http://segment.heiberg.se>). The endocardial contours were drawn on cine CMR to calculate RVEDV, RVESV and RVEF²¹.

The right atrial (RA) size in end-systole was delineated in cine CMR to provide an indication of RV diastolic pressures. The pulmonary artery was segmented on flow CMR to quantify pulmonary regurgitant volume as the backward volume in diastole²² and RF in percent of forward flow. LGE-CMR was visually scored by two experienced observers (MC and HA) in consensus. The RV was divided into 3 short axis and 3 transversal regions giving a total of 9 segments as previously described²². Each segment was given a score from 0-4, no fibrosis was given the score 0, 1-25% segmental fibrosis 1, 26-50% 2, 51-75 % 3 and 76-100% 4. Fibrosis had to be present in two different imaging planes to be considered a true finding. Percent fibrosis of the RV was calculated as $(\text{total score}/36) \times 100\%$.

Statistical analysis:

All statistical analyses were performed with Graphpad Prism v 5.01. All continuous variables were expressed as mean \pm SD. The Mann-Whitney test was used to compare continuous variables in the restrictive versus non-restrictive RV physiology groups and fibrotic versus non-fibrotic groups. Fisher's exact test was used when comparing non-continuous variables between the groups and the odds ratio (OR) with confidence interval (CI) was calculated. Pearson's correlation analysis was performed between the degree of RVOT fibrosis and

RVEDV, RVESV, RVEF and regurgitant volume. Results with a p value <0.05 were considered significant.

RESULTS

Restrictive RV physiology

Percentage end-diastolic forward flow of total flow was $1.10 \pm 0.71\%$ in healthy subjects and therefore the upper normal limit was 2.5%. 16 patients had end-diastolic forward flow $\geq 2.5\%$ and was considered to have restrictive physiology using CMR. The diastolic forward flow as percentage of stroke volume in all patient was $4.7 \pm 6.3\%$, in patients with restrictive physiology $9.1 \pm 5.4\%$ and in patients with non-restrictive physiology $-0.5 \pm 2.9\%$. Most patients with restrictive physiology (n=14) demonstrated negative PA flow at the onset of the distinct end-diastolic flow wave as exemplified in Figure 1C. On Doppler echocardiography 15 patients were found to be restrictive. Ten of these were restrictive also on CMR. On Doppler echocardiography 16 patients were non-restrictive. Ten of these were non-restrictive on CMR. The kappa value between CMR and Doppler echocardiography for restrictive physiology was 0.29, the odds ratio was not significant (OR 3.3, CI 0.8-14.6, p=0.16).

Restrictive RV physiology and RV myocardial fibrosis

Four patients were excluded from the fibrotic vs. non-fibrotic analysis due to inadequate or incomplete LGE-CMR acquisition. Fibrosis of the RVOT on LGE-CMR (Figures 2 and 3) was found in 16 out of 27 (59%) investigated patients. There was a strong association between RVOT fibrosis on LGE-CMR and restrictive RV physiology on CMR (OR 70, CI 5.6-882.7, p<0.001), Table 1. Fourteen of the 16 patients with RVOT fibrosis showed restrictive RV physiology and only one of the 11 patients without RVOT fibrosis showed restrictive RV physiology. Fifteen of the patients with fibrosis had restrictive physiology when using visual assessment and five of the non-fibrotic patients had non-restrictive

physiology. The odds ratio for visual assessment of restrictive physiology and fibrosis was 12.5 (CI 1.2-130.7, $p=0.03$).

However, if using Doppler Echocardiography only 10 patients of the sixteen with fibrosis showed restrictive physiology. Three of the patients without fibrosis showed restrictive physiology on Echocardiography (OR 4.4, CI 0.8-24.0, $p=0.12$).

Fibrosis at the location of the VSD patch in the basal part of the septum was seen in 87% (22 out of 27 patients). Furthermore minimal fibrosis could be seen at the inferoseptal RV insertion point to the LV in 3 patients, in apical trabeculation in 1 patient and in the RV free wall in 1 patient.

Table 2 shows the clinical data of patients with and without RVOT fibrosis. Of note, the incidence of transannular patch (TAP) repair did not differ between the groups ($p=0.37$).

There was a positive correlation between degree of RV fibrosis and RVEF ($p<0.01$), RVEDV, RVESV and regurgitant volume ($p<0.001$ for all), Figure 4. RA size was higher in the group with fibrosis ($p=0.046$) indicating higher RV diastolic pressure (Table 2).

Patients with restrictive physiology had larger RVEDV/BSA ($159\pm 49\text{ml/m}^2$, $p=0.003$), RVESV/BSA ($83\pm 34\text{ ml/m}^2$, $p=0.008$) and higher RF ($45\pm 9\%$, $p=0.003$) compared to patients with non-restrictive physiology on CMR ($111\pm 29\text{ ml/m}^2$, $52\pm 18\text{ ml/m}^2$, $23\pm 19\%$), Table 3.

DISCUSSION

This study is the first to show that there is a strong association between restrictive RV physiology and fibrosis of the RVOT in children after TOF repair with residual postoperative PR. RVOT fibrosis correlated positively to RV volumes and PR but did not relate to TAP repair.

Fibrosis and restrictive physiology

Fibrosis of the RVOT was associated with restrictive physiology assessed by CMR and the link may be that the fibrosis decreases the RV compliance. In an RV with low compliance atrial systole will pump against a stiff RV resulting in forward pulmonary flow in ventricular diastole. Only 1 out of 15 patients with restrictive physiology showed no sign of fibrosis in the RV. Fibrosis was mainly found in the anterior free wall of the RVOT. Furthermore, fibrosis in the region of the VSD repair was seen in most patients and in the inferoseptal RV insertion points or in RV trabeculae in a minority of patients. Previous studies in adults have found RVOT fibrosis in 71-99% after primary repair of TOF^{17, 23} in line with our findings. Extensive RV fibrosis ($\geq 75^{\text{th}}$ percentile) has earlier been associated with restrictive RV physiology in adults¹⁷. In our study in children, we found a clear association with restrictive RV physiology even when including milder degrees of RVOT fibrosis. This difference may be attributed to the younger population in our material as previously proposed¹⁷. In our population patients with fibrosis also had larger RA size indicating higher RA pressure and therefore higher RV diastolic pressure. Restrictive physiology was originally described as patients with end-diastolic forward flow through the pulmonary valve during atrial contraction due to a stiff and non-compliant hypertrophied RV wall. Hence, RV restrictive physiology in the early and midterm postoperative period protects the RV from dilatation and minimizes the effects of PR and this may be the reason that postoperative PR is well tolerated initially after TOF repair²⁴. In our patient population, at 9.2 ± 2.9 years after repair, we found end-diastolic forward flow through the pulmonary valve in patients with fibrosis of the RVOT coupled to higher PR and larger RV volumes. Furthermore, we found a positive correlation with the degree of fibrosis and RV volumes in line with previous studies^{17, 23}. This indicates that the protective nature of restrictive RV physiology early after TOF repair previously described^{19, 25-26} may attenuate with time^{14, 17, 27-28} and fibrosis development may represent the substrate for the secondary form of restrictive RV physiology suggested by Lee et al¹². Therefore, the

etiology of the restrictive physiology in our patient population may be different to the “classical” description. Lee et al divided the patient groups according to restrictive physiology and RV volumes, and found that forward end-diastolic flow was present in both large and small RVs but was associated with better physical exercise tolerance only in conjunction with small RVs¹². This could explain why some previous studies have found restrictive physiology to be a positive prognostic factor^{12, 24} and other studies have shown that restrictive physiology is coupled to reduced RVEF²⁹ and low quality of life³⁰.

We found slightly higher end-diastolic forward flow in restrictive patients (9% of SV) compared to earlier studies (6%)¹¹⁻¹² and this is probably explained by different definitions of restrictive physiology between the studies. We used 2.5% end-diastolic forward flow as cut-off for restrictive physiology based on the forward flow seen in healthy children due to longitudinal AV-plane movement during atrial contraction²⁰.

The association of restrictive physiology and RV fibrosis in our patient population does not necessarily mean that RV fibrosis is the cause of restrictive physiology. However, our findings show that restrictive physiology found at follow up in patients with large RV volumes and RF is strongly associated with myocardial fibrosis in the RVOT.

The agreement between CMR and Doppler-echocardiography was fair (kappa value 0.29) which is similar to the findings of Lee et al (kappa value 0.35 calculated from the published results). A possible explanation for this difference is that CMR averages several cardiac and respiratory cycles and can therefore be viewed as more inclusive for restrictive physiology¹². CMR has been proposed to be more accurate compared to Doppler in the detection of restrictive physiology in dilated pulmonary arteries lacking laminar flow patterns¹⁰.

Cause of fibrosis

The cause of RVOT fibrosis is not clear, but several mechanisms have been proposed, such as the long-term effects of preoperative hypoxemia^{17, 31}. Dilatation of the RV caused by PR has been postulated to be one cause of progressive fibrosis¹⁷ and we have showed a positive correlation between the degree of RVOT fibrosis and PR as well as RV dilatation (Figure 4). However, cause and effect could be reverse with RV fibrosis causing RV dilatation and thereby worsening of the PR. Wald *et al.* showed that the fibrosis is associated with dyskinesia, aneurysmatic dilatation of the RVOT and conduction delay²². PR volume is mainly determined by the size of the pulmonary valvular orifice which may become enlarged in RVOT fibrosis as the pulmonary annulus is connected to the RVOT myocardium³²⁻³³. One possible mechanism for RVOT fibrosis may be that the muscular resection of the infundibulum at repair imposes damages to the microvasculature causing fibrosis development and thereby contributes to restrictive RV physiology²⁸. All patients in our study were repaired via transatrial or transpulmonary approach with only minimal ventricular incisions made in patients with TAP with the aim of preserving the RV infundibulum³⁴. Interestingly, in the study by Wald *et al.* fibrosis was found extending to the anterior RV free wall and neighboring segments where surgery had not taken place²² and this was also found in our material. Therefore, it is possible that fibrosis caused by RV volume overload may co-exist with the surgically related substrates for fibrosis in RVOT creating RV dysfunction. There was no difference in fibrosis development or restrictive RV physiology between the early and late repaired group in the present study and this may be attributed to an over-all earlier repair age compared to previous studies^{17, 23}. There were no differences in cross-clamp times at repair between the fibrotic and the non-fibrotic groups. This indicates that prolonged myocardial hypoperfusion during surgery is not a cause for fibrosis. Consequently, neither long-term effects of hypoxemia, TAP nor ventriculotomies are likely to be the cause of the RVOT fibrosis in children after TOF repair.

Interestingly, we did not find any LGE in four patients with TAP. In our material the patch material used for TAP consisted of the pericardium and the size was quite small (5-10 mm including the supra- and subvalvular parts) which may explain why CMR “missed” to detect LGE in this region.

Limitations

The lack of fibrosis in the RVOT on LGE-CMR does not exclude the existence of a more diffusely spread fibrosis throughout the entire RV wall not detected. LGE-CMR lacks spatial resolution to detect very small areas of fibrosis and the use of an inversion-recovery pulse does not permit the detection of evenly distributed diffuse intercellular fibrosis³⁵. Further studies using high-resolution T1-mapping to quantify the extracellular volume fraction³⁶⁻³⁷ may provide information on the relationship of increased amount of diffuse fibrosis and restrictive physiology. In this study, fibrosis detection was performed by two experienced observers in consensus with visual scoring. Better image quality with higher resolution and better signal-to-noise ratio would be needed for a semi-automatic quantification as used in left ventricular infarct quantification³⁸. The number of patients in the study is fairly limited, which may explain why we did not find a statistically significant relationship between restrictive physiology on Doppler-echocardiography and fibrosis on LGE-CMR and the comparisons of cross-clamp times.

Conclusion

To our knowledge this study is the first showing an association between restrictive RV physiology and RVOT fibrosis visualized on LGE-CMR in children repaired for TOF. The cause for fibrosis still remains unclear and needs to be further addressed in future studies.

Acknowledgements: Annica Maxedius is greatly appreciated for help with patient administration. This study was supported by a grant from the Swedish Heart Lung foundation

REFERENCES:

1. Hamada H, Terai M, Jibiki T, Nakamura T, Gatzoulis MA, Niwa K. Influence of early repair of tetralogy of fallot without an outflow patch on late arrhythmias and sudden death: a 27-year follow-up study following a uniform surgical approach. *Cardiol Young* 2002;**12**(4):345-51.
2. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, *et al.* Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg* 2009;**35**(1):156-64; discussion 164.
3. Pokorski RJ. Long-term survival after repair of tetralogy of Fallot. *J Insur Med* 2000;**32**(2):89-92.
4. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, *et al.* Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med* 1993;**329**(9):593-9.
5. Tamesberger MI, Lechner E, Mair R, Hofer A, Sames-Dolzer E, Tulzer G. Early primary repair of tetralogy of fallot in neonates and infants less than four months of age. *Ann Thorac Surg* 2008;**86**(6):1928-35.
6. Vohra HA, Adamson L, Haw MP. Is early primary repair for correction of tetralogy of Fallot comparable to surgery after 6 months of age? *Interact Cardiovasc Thorac Surg* 2008;**7**(4):698-701.
7. Owen AR, Gatzoulis MA. Tetralogy of Fallot: Late outcome after repair and surgical implications. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2000;**3**:216-226.

8. Norgard G, Gatzoulis MA, Josen M, Cullen S, Redington AN. Does restrictive right ventricular physiology in the early postoperative period predict subsequent right ventricular restriction after repair of tetralogy of Fallot? *Heart* 1998;**79**(5):481-4.
9. Norgard G, Gatzoulis MA, Moraes F, Lincoln C, Shore DF, Shinebourne EA, *et al.* Relationship between type of outflow tract repair and postoperative right ventricular diastolic physiology in tetralogy of Fallot. Implications for long-term outcome. *Circulation* 1996;**94**(12):3276-80.
10. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. *J Am Coll Cardiol* 1996;**28**(7):1827-35.
11. van den Berg J, Wielopolski PA, Meijboom FJ, Witsenburg M, Bogers AJ, Pattynama PM, *et al.* Diastolic function in repaired tetralogy of Fallot at rest and during stress: assessment with MR imaging. *Radiology* 2007;**243**(1):212-9.
12. Lee W, Yoo SJ, Roche SL, Kantor P, van Arsdell G, Park EA, *et al.* Determinants and functional impact of restrictive physiology after repair of tetralogy of Fallot: New insights from magnetic resonance imaging. *Int J Cardiol* 2012.
13. Weber OM, Higgins CB. MR evaluation of cardiovascular physiology in congenital heart disease: flow and function. *J Cardiovasc Magn Reson* 2006;**8**(4):607-17.
14. Bouzas B, Kilner PJ, Gatzoulis MA. Pulmonary regurgitation: not a benign lesion. *Eur Heart J* 2005;**26**(5):433-9.
15. Prakash A, Powell AJ, Krishnamurthy R, Geva T. Magnetic resonance imaging evaluation of myocardial perfusion and viability in congenital and acquired pediatric heart disease. *Am J Cardiol* 2004;**93**(5):657-61.

16. Harris MA, Johnson TR, Weinberg PM, Fogel MA. Delayed-enhancement cardiovascular magnetic resonance identifies fibrous tissue in children after surgery for congenital heart disease. *J Thorac Cardiovasc Surg* 2007;**133**(3):676-81.
17. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, *et al.* Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. *Circulation* 2006;**113**(3):405-13.
18. Muzzarelli S, Ordovas KG, Cannavale G, Meadows AK, Higgins CB. Tetralogy of Fallot: impact of the excursion of the interventricular septum on left ventricular systolic function and fibrosis after surgical repair. *Radiology* 2011;**259**(2):375-83.
19. Gatzoulis MA, Norgard G, Redington AN. Biventricular long axis function after repair of tetralogy of Fallot. *Pediatr Cardiol* 1998;**19**(2):128-32.
20. Kozerke S, Schwitter J, Pedersen EM, Boesiger P. Aortic and mitral regurgitation: quantification using moving slice velocity mapping. *J Magn Reson Imaging* 2001;**14**(2):106-12.
21. Carlsson M, Ugander M, Heiberg E, Arheden H. The quantitative relationship between longitudinal and radial function in left, right, and total heart pumping in humans. *Am J Physiol Heart Circ Physiol* 2007;**293**(1):H636-44.
22. Wald RM, Haber I, Wald R, Valente AM, Powell AJ, Geva T. Effects of regional dysfunction and late gadolinium enhancement on global right ventricular function and exercise capacity in patients with repaired tetralogy of Fallot. *Circulation* 2009;**119**(10):1370-7.
23. Oosterhof T, Mulder BJ, Vliegen HW, de Roos A. Corrected tetralogy of Fallot: delayed enhancement in right ventricular outflow tract. *Radiology* 2005;**237**(3):868-71.

24. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation* 1995;**92**(2):231-7.
25. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, *et al.* Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet* 2000;**356**(9234):975-81.
26. Munkhammar P, Cullen S, Jogi P, de Leval M, Elliott M, Norgard G. Early age at repair prevents restrictive right ventricular (RV) physiology after surgery for tetralogy of Fallot (TOF): diastolic RV function after TOF repair in infancy. *J Am Coll Cardiol* 1998;**32**(4):1083-7.
27. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. *J Am Coll Cardiol* 2004;**43**(6):1068-74.
28. Uebing A, Gibson DG, Babu-Narayan SV, Diller GP, Dimopoulos K, Goktekin O, *et al.* Right ventricular mechanics and QRS duration in patients with repaired tetralogy of Fallot: implications of infundibular disease. *Circulation* 2007;**116**(14):1532-9.
29. Sun AM, AlHabshan F, Cheung M, Bronzetti G, Redington AN, Benson LN, *et al.* Delayed onset of tricuspid valve flow in repaired tetralogy of Fallot: an additional mechanism of diastolic dysfunction and interventricular dyssynchrony. *J Cardiovasc Magn Reson* 2011;**13**:43.
30. Lu JC, Cotts TB, Agarwal PP, Attili AK, Dorfman AL. Relation of right ventricular dilation, age of repair, and restrictive right ventricular physiology with patient-reported quality of life in adolescents and adults with repaired tetralogy of fallot. *Am J Cardiol* 2010;**106**(12):1798-802.

31. Reddy S, Osorio JC, Duque AM, Kaufman BD, Phillips AB, Chen JM, *et al.* Failure of right ventricular adaptation in children with tetralogy of Fallot. *Circulation* 2006;**114**(1 Suppl):I37-42.
32. Gross L, Kugel MA. Topographic Anatomy and Histology of the Valves in the Human Heart. *Am J Pathol* 1931;**7**(5):445-474 7.
33. Bartelings MM, Bogers AJ, Galantowicz ME, Gittenberger-De Groot AC. Anatomy of the aortic and pulmonary roots. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 1998;**1**:157-164.
34. Morales DL, Zafar F, Fraser CD, Jr. Tetralogy of Fallot repair: the Right Ventricle Infundibulum Sparing (RVIS) strategy. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 2009:54-8.
35. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. *Circ Cardiovasc Imaging*;3(6):727-34.
36. Arheden H, Saeed M, Higgins CB, Gao DW, Bremerich J, Wyttenbach R, *et al.* Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with ^{99m}Tc-DTPA autoradiography in rats. *Radiology* 1999;**211**(3):698-708.
37. Ugander M, Oki AJ, Hsu LY, Kellman P, Greiser A, Aletras AH, *et al.* Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. *Eur Heart J* 2012.
38. Heiberg E, Ugander M, Engblom H, Gotberg M, Olivecrona GK, Erlinge D, *et al.* Automated quantification of myocardial infarction from MR images by accounting for partial volume effects: animal, phantom, and human study. *Radiology* 2008;**246**(2):581-8.

TABLES

Table 1. Relationship between restrictive RV physiology detected on CMR and RVOT fibrosis detected on LGE-CMR

	Patients with fibrosis (n=16)	Patients with no fibrosis (n=11)	
Restrictive RV physiology detected on CMR (n=15)	14	1	P<0.001 OR= 70.0 (CI 5.6-882.7)
Non-restrictive RV physiology detected on CMR (n=12)	2	10	

Table 2. Patient characteristics in patients with and without fibrosis.

	All patients (n= 27)	Patients with fibrosis in RVOT (n=16)	Patients without fibrosis in RVOT (n=11)	p values
Age (years)	10.2±2.6	10.5±2.5	9.8±2.8	0.73
Follow up time (years)	9.2±2.7	9.3±2.7	9.0±2.7	0.98
BSA (m ²)	1.2±0.3	1.2±0.3	1.1±0.3	0.69
Females (%)	48	50	45	
Age at repair (years)	0.8±0.8	0.9±0.9	0.7±0.4	0.29
repair < 6 months (%)	37	31	44	
TAP (%)	52	56	36	0.37
RVEDV ml/m ²	134 ± 50	158 ± 47	100±31	0.002
RVESV ml/m ²	67±33	83±33	44±17	0.002
RV EF %	52±7	49±8	56±5	0.18
RF, ml	29±24	36±23	17±22	0.02
RF, ml/BSA	23±16	30±14	12±17	0.02
RF, %	33±19	40±16	22±19	0.02
RA ml/m ²	46±12	50±12	40±12	0.046
Transatrial approach (%)	100	100	100	1.0
Cross-clamp time (min)	49±17	49±10	49±25	0.32
Hospital stay (days)	13±6	14±7	12±5	0.50
Need for PVR surgery on follow up	41	56	18	0.07

Table 3. Patient characteristics in patients with and without restrictive physiology detected on CMR.

	All patients (n= 31)	Patients with restrictive physiology (n=16)	Patients without restrictive physiology (n=15)	p values
RVEDV/BSA ml/m ²	136±47	159±49	111±29	0.003
RVESV/BSA ml/m ²	68±31	83±34	52±18	0.008
RVSV/BSA ml/m ²	68±18	76±19	59±13	0.005
RVEF	52±7	49±8	54±6	0.07
RF (ml)	29±22	39±21	18±20	0.005
RF/BSA (ml/m ²)	25±16	33±11	16±16	0.003
RF (%)	35±18	45±9	23±19	0.003

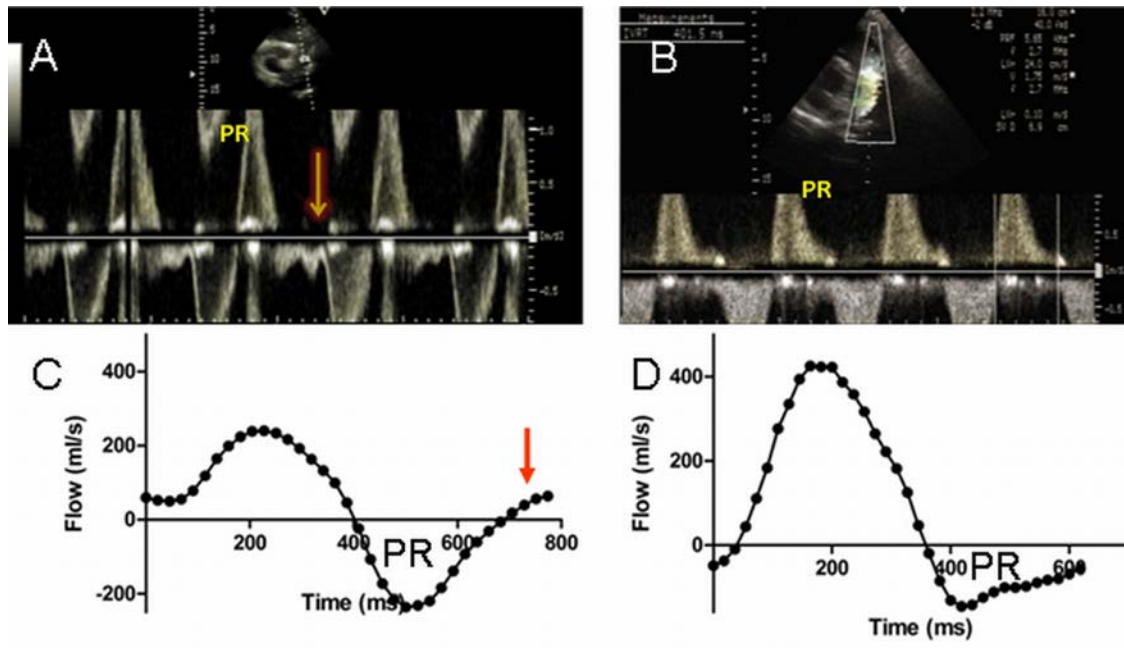


Figure 1: Doppler echocardiography (top) and CMR (bottom) examples of restrictive RV physiology (A and C) and non-restrictive RV physiology (B and D) in patients with pulmonary regurgitation (PR). The red arrows point to the end-diastolic forward flow signal in the pulmonary artery which is used as a marker for restrictive RV physiology.

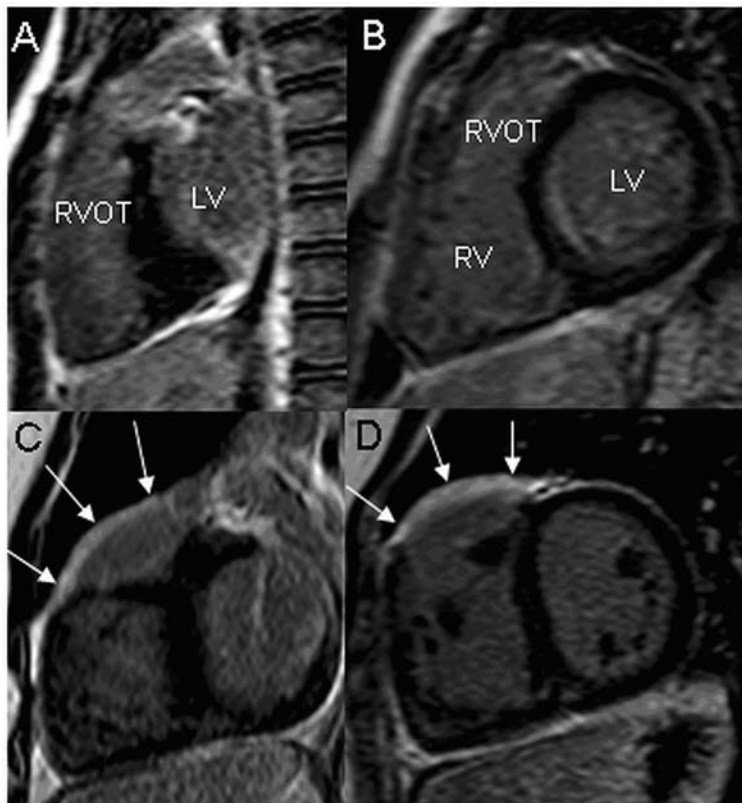


Figure 2: Late gadolinium enhancement CMR of one patient without (upper panel) and with (lower panel) fibrosis of the RVOT. Viable myocardium is depicted black and fibrosis hyperenhanced or white (white arrows in C and D) by late gadolinium enhancement CMR. A and C show the heart in oblique sagittal RVOT views and in B and D short axis views. Fibrosis had to be visualized in two projections to be counted as a positive finding.

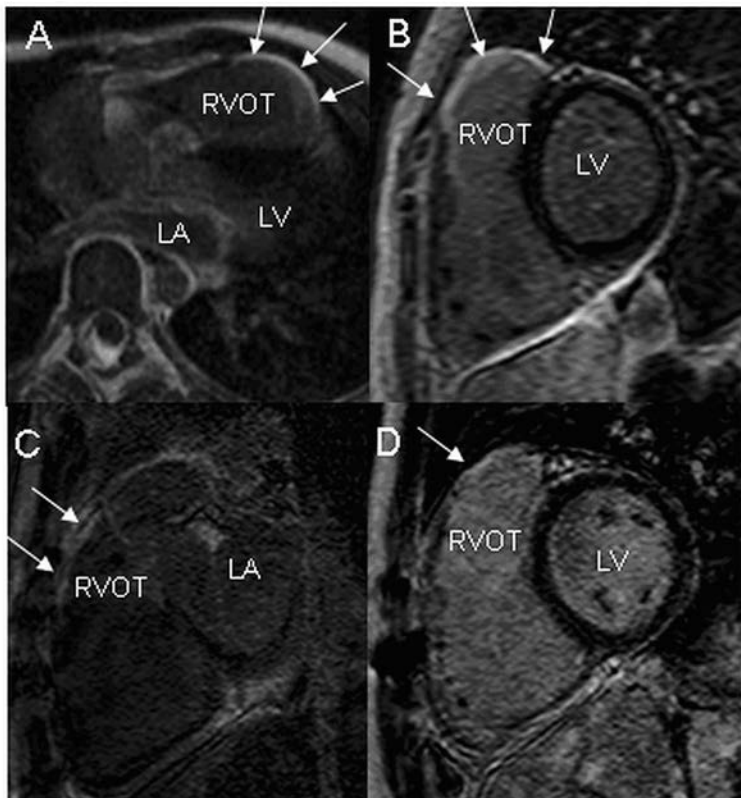


Figure 3: Two patients without previous TAP repair showing fibrosis of the RVOT (white arrows). Patient 1 (A and B) have extensive transmural fibrosis seen in the transversal view (A) and short axis view (B). In A, note that the right part of the RVOT does not show any sign of fibrosis. Patient 2 (C and D) also show transmural fibrosis in parts of the RVOT.

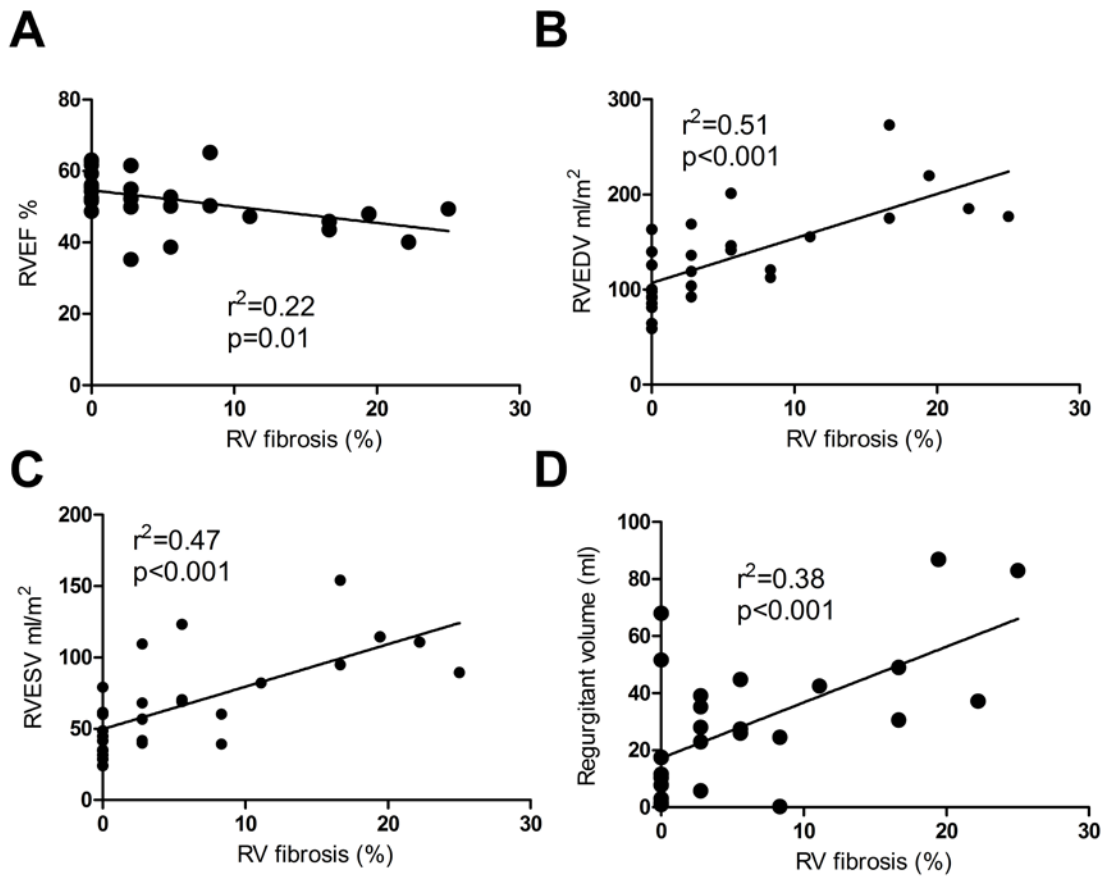


Figure 4. Correlation between the degree of fibrosis and **A** right ventricular ejection fraction (RVEF), **B** right ventricular end-diastolic volume (RVEDV) indexed to BSA, **C** right ventricular end-systolic volume (RVESV) indexed to BSA and **D** pulmonary regurgitant volume.

APPENDIX . MR sequence parameters.**Cine:**

Philips: A steady-state free-precession sequence with retrospective ECG triggering was used with acquired temporal resolution of typically 47 ms reconstructed to 25 ms, echo time 1.4 ms, flip angle 60° and 8 mm slice thickness. Siemens: A gradient-echo sequence with prospective ECG triggering was used with typically 15 phases per cardiac cycle, with acquired temporal resolution of 100 ms reconstructed using echo sharing reconstructed to every 50 ms, echo time 4.8 ms, flip angle 30° and 10 mm slice thickness. Breath-hold times were typically 15 seconds.

Flow:

Philips: A fast field echo velocity encoded sequence with retrospective ECG triggering was used with repetition time 10 ms, echo time 5 ms, flip angle 15°, slice thickness 6 mm, 35 phases, number of acquisitions 1, no parallel imaging and a velocity encoding gradient (VENC) of 200 cm/s.

Siemens: Imaging parameters were the same as above except that the images were obtained with prospective ECG triggering. Velocity information was acquired over two heartbeats to quantify the flow during the end of diastole.

The flow sequences were non-segmented without echo sharing with an acquired temporal resolution of 20 ms for Philips and 35 ms for Siemens.

Late gadolinium enhancement

Philips: An inversion-recovery balanced turbo field echo sequence with slice thickness, 8 mm; field of view, 340 mm; matrix, 126 x 256; repetition time, 3.14 ms; echo time, 1.58 ms was used.

Siemens: An inversion-recovery turbo fast low-angle shot sequence with slice thickness, 10 mm; field of view, 380 mm; matrix, 126 x 256; flip angle, 25°; repetition time, 100 ms; echo time, 4.8 ms was used.

The inversion time was manually adjusted to null the signal from the non-fibrotic myocardium and images were acquired at end-diastole.