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

2013

Citation for published version (APA):

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.
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 ± 2.8) were included 9.2±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 good. Age at repair has gradually decreased since the early era of TOF surgery without increase in mortality or need for re-intervention. 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). 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 echocardiography.

Restrictive RV physiology in the setting of significant PR has been shown to be of positive prognostic value at mid term follow-up 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 physiology. Thus, CMR has become a valuable tool in the assessment of patients operated for TOF. 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). 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 described 19. 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 displacement\(^{20}\). 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 RVEF. 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 diastole 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 described. 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 (total score/36)x100%.

**Statistical analysis:**

All statistical analyses were performed with Graphpad Prism v 5.01. All continuous variables were expressed as mean ± 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±0.71% in healthy subjects and therefore the upper normal limit was 2.5%. 16 patients had end-diastolic forward flow ≥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±6.3%, in patients with restrictive physiology 9.1±5.4% and in patients with non-restrictive physiology -0.5±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±49ml/m², p=0.003),
RVESV/BSA (83±34 ml/m², p=0.008) and higher RF (45±9%, p=0.003) compared to patients
with non-restrictive physiology on CMR (111±29 ml/m², 52±18 ml/m², 23±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 (≥75\(^{th}\) percentile) has earlier been associated with restrictive RV physiology in adults \(^{17}\). 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 proposed \(^{17}\). 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 repair \(^{24}\). 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 al\(^{12}\). 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 RVs. This could explain why some previous studies have found restrictive physiology to be a positive prognostic factor and other studies have shown that restrictive physiology is coupled to reduced RVEF and low quality of life.

We found slightly higher end-diastolic forward flow in restrictive patients (9% of SV) compared to earlier studies (6%) 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 contraction.

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-echochardiography 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 physiology. CMR has been proposed to be more accurate compared to Doppler in the detection of restrictive physiology in dilated pulmonary arteries lacking laminar flow patterns.

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\textsuperscript{17, 31}. Dilatation of the RV caused by PR has been postulated to be one cause of progressive fibrosis\textsuperscript{17} 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 dys-/akinesia, aneurysmatic dilatation of the RVOT and conduction delay\textsuperscript{22}. 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 myocardium\textsuperscript{32-33}. 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 physiology\textsuperscript{28}. 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 infundibulum\textsuperscript{34}. 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 place\textsuperscript{22} 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\textsuperscript{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 supravalvular 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 fibrosis\(^\text{35}\). Further studies using high-resolution T1-mapping to quantify the extracellular volume fraction\(^\text{36-37}\) 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 quantification\(^\text{38}\). 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:


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

<table>
<thead>
<tr>
<th></th>
<th>Patients with fibrosis (n=16)</th>
<th>Patients with no fibrosis (n=11)</th>
<th>P&lt;0.001 OR= 70.0 (CI 5.6-882.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrictive RV physiology</td>
<td>14</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>detected on CMR (n=15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-restrictive RV physiology</td>
<td>2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>detected on CMR (n=12)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Patient characteristics in patients with and without fibrosis.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n= 27)</th>
<th>Patients with fibrosis in RVOT (n=16)</th>
<th>Patients without fibrosis in RVOT (n=11)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.2±2.6</td>
<td>10.5±2.5</td>
<td>9.8±2.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Follow up time (years)</td>
<td>9.2±2.7</td>
<td>9.3±2.7</td>
<td>9.0±2.7</td>
<td>0.98</td>
</tr>
<tr>
<td>BSA (m$^2$)</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Females (%)</td>
<td>48</td>
<td>50</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age at repair (years)</td>
<td>0.8±0.8</td>
<td>0.9±0.9</td>
<td>0.7±0.4</td>
<td>0.29</td>
</tr>
<tr>
<td>repair &lt; 6 months (%)</td>
<td>37</td>
<td>31</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>TAP (%)</td>
<td>52</td>
<td>56</td>
<td>36</td>
<td>0.37</td>
</tr>
<tr>
<td>RVEDV ml/m$^2$</td>
<td>134 ± 50</td>
<td>158 ± 47</td>
<td>100±31</td>
<td>0.002</td>
</tr>
<tr>
<td>RVESV ml/m$^2$</td>
<td>67±33</td>
<td>83±33</td>
<td>44±17</td>
<td>0.002</td>
</tr>
<tr>
<td>RV EF %</td>
<td>52±7</td>
<td>49±8</td>
<td>56±5</td>
<td>0.18</td>
</tr>
<tr>
<td>RF, ml</td>
<td>29±24</td>
<td>36±23</td>
<td>17±22</td>
<td>0.02</td>
</tr>
<tr>
<td>RF, ml/BSA</td>
<td>23±16</td>
<td>30±14</td>
<td>12±17</td>
<td>0.02</td>
</tr>
<tr>
<td>RF, %</td>
<td>33±19</td>
<td>40±16</td>
<td>22±19</td>
<td>0.02</td>
</tr>
<tr>
<td>RA ml/m$^2$</td>
<td>46±12</td>
<td>50±12</td>
<td>40±12</td>
<td>0.046</td>
</tr>
<tr>
<td>Transatrial approach (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>1.0</td>
</tr>
<tr>
<td>Cross-clamp time (min)</td>
<td>49±17</td>
<td>49±10</td>
<td>49±25</td>
<td>0.32</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>13±6</td>
<td>14±7</td>
<td>12±5</td>
<td>0.50</td>
</tr>
<tr>
<td>Need for PVR surgery on follow up</td>
<td>41</td>
<td>56</td>
<td>18</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Table 3. Patient characteristics in patients with and without restrictive physiology detected on CMR.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=31)</th>
<th>Patients with restrictive physiology (n=16)</th>
<th>Patients without restrictive physiology (n=15)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVEDV/BSA ml/m²</td>
<td>136±47</td>
<td>159±49</td>
<td>111±29</td>
<td>0.003</td>
</tr>
<tr>
<td>RVESV/BSA ml/m²</td>
<td>68±31</td>
<td>83±34</td>
<td>52±18</td>
<td>0.008</td>
</tr>
<tr>
<td>RVSV/BSA ml/m²</td>
<td>68±18</td>
<td>76±19</td>
<td>59±13</td>
<td>0.005</td>
</tr>
<tr>
<td>RVEF</td>
<td>52±7</td>
<td>49±8</td>
<td>54±6</td>
<td>0.07</td>
</tr>
<tr>
<td>RF (ml)</td>
<td>29±22</td>
<td>39±21</td>
<td>18±20</td>
<td>0.005</td>
</tr>
<tr>
<td>RF/BSA (ml/m²)</td>
<td>25±16</td>
<td>33±11</td>
<td>16±16</td>
<td>0.003</td>
</tr>
<tr>
<td>RF (%)</td>
<td>35±18</td>
<td>45±9</td>
<td>23±19</td>
<td>0.003</td>
</tr>
</tbody>
</table>
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 points at 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.