ORIGINAL ARTICLE

Mid-term follow-up of pulmonary regurgitation in repaired asymptomatic TOF patients by transannular patch: A prospective cardiac MRI study

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Abstract  Objective: The long-term outcome of Tetralogy of Fallot (TOF) surgical repair in developing countries is still unknown. Therefore the aim of the study was the quantification of pulmonary regurgitation (PR) and right ventricular functions using cardiac magnetic resonance (CMR) in order to follow up midterm post transannular patch repair of asymptomatic TOF patients.

Methods: We prospectively studied 37 asymptomatic corrected TOF patients (aged 18 years or less), aged at surgery was of median, min/max of (19, 8/48 months). Cardiac functions were assessed using routine steady state free precession techniques. PR quantification was performed using the routine velocity encoding phase contrast in the main pulmonary artery.

Results: Four patients had mild PR, 26 had moderate PR and seven had severe PR, with a median value of PR% in CMR amounting to 29% (max: 75% and min: 13%). Indexed right ventricle end-diastolic volume amounted to (mean ± SD) 130 ± 38 ml, and indexed right ventricle end-systolic volume amounted to 63 ± 26 ml.

Conclusion: Accurate quantitative assessment of PR in the mid and long-term course of TOF patients is paramount. CMR has to be introduced as a new modality in Egypt in the follow up course of asymptomatic TOF patients.

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1. Introduction

Tetralogy of Fallot (TOF) is the most common congenital cyanotic heart disease. Correction of TOF can be performed with low mortality; therefore a growing population of postsurgical repair TOF patients survives into adulthood (1).
Transannular patch repair is one of the surgical techniques performed to relieve the stenosis of the right ventricular outflow tract (RVOT) or pulmonary annulus, an incision through the pulmonary valve (PV) to open the RVOT. A patch is then used to increase the diameter of the outflow region and the main pulmonary artery (2).

Among the most common complications of TOF surgical repair is pulmonary regurgitation (PR). It remains the most common postrepair lesion influencing earlier morbidities (2,3).

Other complications might include, dilated right ventricle (RV), inter-ventricular interactions with left ventricle (LV) dysfunction (4), pulmonary artery aneurysm or peripheral stenosis of the pulmonary arteries. It can also be associated with exercise intolerance, atrial and ventricular arrhythmia, and sudden cardiac death (5).

Moreover, many studies reported improved RV volumes and function, improved exercise capacity, stabilization of QRS duration after pulmonary valve replacement (PVR). However, a question of debate remains with the optimal timing of PVR in patients with corrected TOF (6).

With the complexity of RV geometry and difficult echocardiographic window of the pulmonary valve, 2D and Doppler echocardiographic measures for quantification of PR and RV function could not be standardized (7).

The long-term outcome of corrected TOF surgery in developing countries is unknown. This might be due to lack of guidelines, recording results, and/or introducing new modalities such as the usage of cardiac magnetic resonance (CMR).

Therefore, it is paramount to follow up those patients postoperatively in the short and long term, and through accurately quantifying PR, cardiac volumes and functions. CMR is now considered the gold standard for non-invasive quantification of PR and RV volumes (7). D’Udekem et al. (5) stated that every TOF should at least have one CMR visit with pulmonary angiography to determine the pulmonary tree anatomy and morphology.

Hence, this study is the first CMR study showing PR and cardiac function in surgically corrected asymptomatic TOF patients using the transannular patch technique in a developing country.

2. Material and methods

The study was approved by Cairo University’s Review Board for Human Research and Ethics. As a routine work protocol in educational hospitals a written informed consent was always obtained from the accompanying parents, according to our institute’s guidelines.

2.1. Subjects

We prospectively studied 37 asymptomatic, clinically stable patients (aged 18 years or less) (Table 1), who had corrective intra-cardiac repair for TOF. They were referred to our postoperative outpatient clinic in Cairo University Children’s Hospital, for regular visits at least once a year.

All patients had transannular patch augmentation of the right ventricular outflow tract in the Cairo University Hospitals. A prior palliative procedure (modified Blalock Taussig (MBT)) shunt was performed in 2 patients. Patients underwent a trans-thoracic echocardiogram for study purposes. Both the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>General demographic and clinical patient characteristics.</th>
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</thead>
<tbody>
<tr>
<td>Parameters</td>
<td>Cases (n = 37)</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>21 (57)</td>
</tr>
<tr>
<td>Females</td>
<td>16 (43)</td>
</tr>
<tr>
<td>Age at examination (years)</td>
<td>9.3 ± 4.8</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Age at surgery (month)</td>
<td>24 (8–48)</td>
</tr>
<tr>
<td>(Median, max, min)</td>
<td></td>
</tr>
<tr>
<td>BSA (m2)</td>
<td>0.9 ± 0.31</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Increased C/T ratio (n, %)</td>
<td>32 (86)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>126.8 ± 19.8</td>
</tr>
<tr>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>RBBB (n, %)</td>
<td>20 (54)</td>
</tr>
<tr>
<td>Previous palliative surgery (MBT shunt) (n, %)</td>
<td>2 (5.4)</td>
</tr>
</tbody>
</table>


Echo and CMR scans were performed within 3 months of each other between December 2011 and April 2013.

2.2. Inclusion criteria

- TOF patients with moderate to severe pulmonary regurgitation diagnosed using echo without symptoms of right ventricular dysfunction or NYHA (I or II).
- Age at operation (mid and long term) following the repair.
- Time of postoperative follow up.
- ECG: prolonged QRS duration (> 120 ms).

2.3. Exclusion criteria

- TOF patients with severe right ventricular dysfunction.
- Uncooperative patients.
- TOF patients who developed major or early postoperative complications.
- TOF patients who developed arrhythmias.
- TOF patients with pacemakers.
- Major or severe congenital anomalies.
- Echo findings including:
  - Residual shunts.
  - Peripheral pulmonary artery stenosis.
- Short term follow-up of patients developing PR within 30 days postoperatively.

2.4. CMR

2.4.1. Patient preparation prior to CMR examination

In all cases, an expert in congenital heart disease CMR (A.K.) spoke to patients and their parents or accompanying adults before the CMR examination. During this visit, the expert explained the CMR examination, took the history, checked for pacemakers or metal in the patients’ body, informed the
patient that one of the parents may accompany the child inside the CMR room. Depending on this conversation with the patient and the parents, the expert and the parents mutually decided whether the patient could be scanned without sedation or not.

2.4.2. CMR protocol

CMR studies were acquired with 1T (Panorama), and 1.5T (Achieva), Philips systems.

Cardiac volumes were done using the steady-state free-precession (SSFP) cine CMR acquisitions (8,9) in short-axis cine imaging from the atroventricular junction through the cardiac apex (TR: 4.2 ms, TE: 2.1 ms, slice thickness: 8 mm and 2 averages). Sense was not used during cardiac volume acquisition.

Phase shift velocity encoding (PC-VENC) (8,9) value was adjusted to 200 cm/s in both the pulmonary artery and aorta. Imaging was performed with a breath-hold technique (15 s per slice level). Typical slice thickness was 6–8 mm. Velocity maps were generated at 20 equidistant cardiac phases (Fig. 1).

PC-VENC with flow-sensitive sequences performed perpendicular to the vessel of interest whether the aorta or the main pulmonary artery. Planning was performed from 2 orthogonal views. The physician responsible for the visit made careful screening of the ECG along the whole sequence. Cases with cardiac rhythm alterations and possibly artifacts also were included to demonstrate routine clinical cases. If more than three untriggered pulses occurred, the sequence was aborted and repeated.

The MPA flow measurement was performed about 1 cm distal (and perpendicular) to the pulmonary valve annulus, to assess the pulmonary regurgitant fraction (RF %), and at the level of MPA in the aorta (Fig. 1).

RF% was calculated by dividing the regurgitant volume across the pulmonary annulus by the total forward volume. PR was graded as mild if RF% on CMR was less than 20%, moderate if it was between 20% and 40%, and severe if it was more than 40%.

End-systolic and end-diastolic volumes were measured by manually tracing the area of the endocardial surfaces, and normalized to the body surface area (BSA) using the Mosteller equation.

Pulmonary angiography was performed using previously described protocols (8,9). A gadolinium based contrast material was injected intravenously, with dosage of 0.15–0.2 mmol/kg. At the beginning of the study, seventeen patients were examined with contrast material in order to obtain pulmonary tree angiography. Later in the study in order to show the pulmonary tree, a stack of 3D SSFP without contrast material injection (8,9) was used in 20 patients instead.

A phased-array sense cardiac coil (5 channels) was used for scanning. Sedation was used, when appropriate.

No general anesthesia was used.

2.5. CMR assessment

Software analysis: A dedicated software [Philips, work station®] calculated SV by subtracting the end-systolic volume [ESV] from the end-diastolic volume [EDV].

Ventricular volumes: Contours were marked manually by a radiologist (A.K.) with 5 years of experience in CMR, at the

![Fig. 1](image-url) Phase contrast velocity encoding (PC-VENC) in pulmonary artery (PA) and aorta (Ao). Upper row shows the regurgitation flow in the pulmonary artery during diastole (arrow) in a Fallot patient postrepair. Lower row represents the flow curves of forward and backward flow in PA (vessel 5) and Ao (vessel 6), they show moderate regurgitant fraction in the PA of 37% and 0% in the Ao. The green line in the flow curves represents the cardiac phases.
boundary between the blood pool and the myocardium. The RV papillary muscles were included in the RV volume.

3. Statistical analysis

All statistical calculations were done using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) v. 21 for Mac. Continuous variables were described using mean ± standard deviation (± SD), median and ranges, when possible. Categorical variables were described using count and percentages. Correlation between various variables was performed using Pearson moment correlation equation. Bland–Altman was drawn to show the upper and lower of agreement between variables.

4. Results

Patient clinical and demographic characteristics are included in Table 1.

The study cohort consisted of 37 patients with TOF at least 1 year after total surgical repair. In all patients, RVOT reconstruction was performed using transannular patch at the Cairo University Hospitals.

Two patients underwent palliative Blalock-Taussig shunt before corrective surgery.

All patients were in NYHA I as well as sinus rhythm with increased QRS duration; mean QRS duration in ECG was 126 ± (19.8) ms.

Twenty (54%) patients had right RBBB and none of the patients had ventricular arrhythmias.

The echo failed in 4 patients due to bad acoustic window; however, they were included in the study as they fulfilled the other inclusion criteria.

Average scan time per study = 35 min.

Seventeen patients were examined with contrast material (Gadolinium based contrast material) and 20 patients without contrast material. Renal functions were checked prior to contrast injection.

4.1. CMR results

Table 2 shows the average, median, max and min of forward flow, backward flow, net flow as well as the regurgitation fraction in the pulmonary artery.

In our cohort, four patients had mild PR, 26 had moderate PR and seven had severe PR, with a median value of RF% in CMR amounting to 29% (max: 75% and min.13%) (Table 3).

Seven patients (19%) had RVEDVI above 150 ml/m². Two of those seven patients had a PR% above 45%.

The right ventricular volumes and function were of mean, min., max. of the EDVI = 130 ml/m² (71–130 ml/m²), ESVI = 63 ml/m² (31–127 ml/m²) and ejection fraction of 52% (36–52%) respectively.

The left ventricular volumes and function were of mean, (min., max.) of the EDVI = 72 ml/m² (93–110 ml/m²), ESVI = 29 ml/m² (11–48 ml/m²) and ejection fraction of 52% (36–52%) respectively.

The differences between forward flow means measured using phase contrast velocity encoding in the pulmonary artery/aorta and the stroke volume measured using the SSFP volumetry of the RV/LV showed statistically insignificant differences of \( p = 0.326, p = 0.415 \) respectively. Fig. 2 shows the upper and lower limits of agreements in an Bland–Altman graph.

Scatter plot graphs (Fig. 3) show the correlation between pulmonary regurgitation volume (PRV) and the end diastolic volume of the right ventricle (indexed to surface body area). Fig. 4 represents the correlation between PR% and the end diastolic volume of the right ventricle (indexed to surface body area).

The correlation between PR% and RVEDV was \( r = 0.562 \). The correlation between PRV and the RVEDV was \( r = 0.697 \).

Negative correlation (\( r = -0.250 \) and \( r = -0.499 \)) was found between the right ventricle ejection fraction and the RVEDV and RVEDVI respectively.

### Table 2 Pulmonary regurgitation fraction.

<table>
<thead>
<tr>
<th></th>
<th>Forward flow (ml)</th>
<th>Backward flow (ml)</th>
<th>Net flow (ml)</th>
<th>PR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>65</td>
<td>25</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>Max.</td>
<td>162</td>
<td>85</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>Min.</td>
<td>28</td>
<td>5</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Median</td>
<td>55</td>
<td>17</td>
<td>37</td>
<td>29</td>
</tr>
</tbody>
</table>

Showing the average, maximum, minimum and median of the forward, backward and net flows measured in the pulmonary artery. Pulmonary regurgitation fraction: PR%.

Seven patients (19%) had RVEDVI above 150 ml/m². Two of those seven patients had a PR% above 45%.

The right ventricular volumes and function were of mean, min., max. of the EDVI = 130 ml/m² (71–130 ml/m²), ESVI = 63 ml/m² (31–127 ml/m²) and ejection fraction of 52% (36–52%) respectively.

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The correlation between PR% and RVEDV was \( r = 0.562 \). The correlation between PRV and the RVEDV was \( r = 0.697 \).

Negative correlation (\( r = -0.250 \) and \( r = -0.499 \)) was found between the right ventricle ejection fraction and the RVEDV and RVEDVI respectively.
A weak correlation ($r_s = 0.036$) was found between the right ventricle ejection fraction and the degree of pulmonary regurgitation.

A strong negative correlation was found between the RV/LV ratio and the RVEF ($r_s = -0.501$).

Ejection fraction of both right and left ventricles showed positive correlation, $r_s = 0.468$, $p < 0.0001$.

5. Discussion

A growing population of surgically corrected TOF patients is now able to survive into adulthood (1). This might represent a challenge in the follow up of such increasing numbers.

Surgical techniques of TOF correction include RVOT muscle resection with a transatrial–transpulmonary approach or transannular patch repair (2). The later is the technique of choice in our developing country.

One of the most important predicting factors for long term outcome after TOF repair in developed countries is the surgical technique of intra- and postoperative management problems (transannular versus pulmonary valve sparing). Residual PR is regarded as an important determinant of outcome for these patients (10), as it may contribute to RV enlargement and dysfunction, exercise intolerance, arrhythmias and an increased risk for sudden cardiac death (11–13).

On the other hand, late total repair surgery, and use of palliative surgery represent additional contributing factors to long-term outcome in developing countries. The lack of follow up data, recorded history or using new techniques also adds to the factors that complicate the post-operative management.

In Egypt, as a developing country, we were aware of the fact that additional factors (other than PR and RV diastolic dysfunction) may influence the long-term outcome of TOF repair. These factors may include intra- and postoperative problems, such as trans-annular instead of pulmonary valve sparing surgery technique, delay in surgical repair, and frequent use of palliative surgery.

In addition, the number of children who received surgical repair of TOF in our country is currently beyond the academic interest. The long-term prognosis of surgically corrected TOF patients is good and has improved with each decade as well. Good strategies, guidelines, follow up intervals and introducing new techniques using CMR are essential.

Moreover, the timing of pulmonary valve replacement is inconsistent in the literature (6). Most studies suggest that pulmonary valve replacement serves in decreasing RV volumes and improves exercise capacity. Long-term consequences and optimal timing for such intervention are incompletely defined. Proper assessment of PR and RV function remains a pillar during follow up, in order to guide each patient’s individual plan for intervention. CMR currently plays an important role in optimizing the timing of valve replacement.

CMR derived measurement is the current gold standard for quantification of PR as well as RV volumes and functions. Currently CMR is more available, with lower expenses, and with the introduction of new CMR techniques, scan duration is much shorter (14). For instance we injected contrast material in some patients at the beginning. Yet in the later cases, with increasing CMR experience, no contrast was used and 3D balanced gradient sequences were used instead in order to view the pulmonary arteries, which reduced costs per patient.

Another important result in this study is that patients above 4.5 years are capable of being studied without need of general anesthesia. The youngest patient in our study was 4.8 years old. Recently we implemented a general rule in our unit, which is that patients are not sent directly to sedation or anesthesia. However, given enough time talking with those young patients, assuring them, and making them attend another scan prior to theirs, reflected that CMR can be performed and successfully answer the clinical question with no sedation or anesthesia (15).

Being familiar with the hemodynamics behind surgically corrected Fallot in specific and congenital heart diseases in general allows good planning of the CMR study (16) which also helps in shortening the duration through performing the essential sequences only. In the current study average scan duration was 35 min.
5.1. Intra-validation of CMR measurements

The results showed that the differences between the blood flow mean measured directly in the pulmonary artery and aorta compared to the calculated stroke volume from the volumetry study are statistically insignificant. Both values were measured using two different techniques and two different sequences. This in turn intra-validates our scanner and the results of the PR quantification.

5.2. Quantification of severity PR using CMR

In the current study a correlation was plotted between PR% and end diastolic volume of the right ventricle (RVEDV) ($r_s = 0.562$). A much better correlation was found between the pulmonary regurge volume (PRV) (backward flow divided by the body surface area) and right ventricle volume ($r_s = 0.697$), demonstrating the effect of large PR% on right ventricular after load i.e. larger end diastolic volumes are associated with larger PR%. Similar findings were recorded in Spiewak et al. (17) who showed correlation of RVEDV with PRF and PRV to reach ($r = 0.430$) and ($r = 0.686$) respectively.

The ejection fraction of the right ventricle was negatively correlated with the indexed end diastolic and systolic volumes, amounting to ($r = -0.499$) and ($r = -0.782$) respectively. Similar findings were recorded by M.Y. Abd El Rahmane et al. (18). He studied 40 corrected TOF patients. The correlation between ejection fraction and volumes was $r = -0.35$ and $r = -0.82$ for the end diastolic and end systolic volumes respectively.

Another positive correlation was found between the ejection fractions of the right and left ventricles ($r_s = 0.42$), which might be due to an inter-ventricular interaction. In Geva et al. (19), the correlation between the ejection fraction of both ventricles was ($r_s = 0.58$).

The weak negative correlation between PR% and RVEF ($r_s = 0.036$) seems to reflect a compensatory mechanism through the increased SV for a developed myocardial dysfunction, in order to maintain relatively normal RVEF at least during earlier postoperative periods. Thus, it appears that CMR can help to diagnose RV dysfunction in clinically asymptomatic patients even before reduction of RVEF (20). In the five clinically silent patients, who had RVEDI above 150 ml/m$^2$, cardiology consultation was recommended in order to consider the PVR.

5.3. CMR and echo

In a study by Agha et al. (21), held in Egypt, a suggested cutoff value of 0.8 for pulmonary regurge index (PRI) and 64 ms for no flow time (NFT) were found to offer the highest specificity and sensitivity in identifying cases with hemodynamically significant PR. It also represented the most reliable prediction for PR severity as well as a highly specific pressure half time (PHT) of $<77$ ms.

However, it was found to be a poorly sensitive index with only 27% sensitivity.

The abovementioned study confirms the fact that despite frequency of using Doppler echocardiography-PR waves to estimate the mean and end-diastolic pulmonary pressure, there is no agreement on a clinically accepted method for quantifying pulmonary regurgitation using colored waved, Doppler (22,23). It confirms the fact that echo cutoff values might differ from one center to the other, as well as from one country to the other. On the other hand, CMR is able to provide solid patient follow up results that will not show much variability between different centers.

We recommend that patients with TOF postrepair in our country to be examined with CMR at least once during their postoperative course. It might help to unmask RV dysfunction in asymptomatic TOF patients long after repair, provide an accurate tool to determine longer-term prognosis in presence of severe PR and good functional capacity, through accurate assessment of the ventricular volumes and functions, measure PR percentage and provide records to follow up those patients.

It also demonstrated good results of transannular patch surgical technique in long term follow up of those patients in our country. Further CMR studies in our country are required to follow up patients’ prognosis, and survival rate.

5.4. Study limitations

Limitations of the study could be summarized in the small number of patients included. However, in our developing country the role of CMR is not well developed and the echo is still the modality of choice due to economic status. Another limitation was the usage of two different magnets, as at the start of the study the CMR package was not available in the Cairo University and nine patients had the CMR in a private center on one tesla Philips machine, yet the difference between magnets is not expected to influence the results especially that a single observer (A.K.) performed and processed all patients.

6. Conclusion

Accurate quantitative assessment of PR in the mid and long-term course of TOF patients is paramount. CMR has to be introduced as a new modality in Egypt in the follow up course of asymptomatic TOF patients.

Conflict of interest

The author has no conflict of interest.

Author contribution

The Author A.K. has performed the patients’ CMR scans, performed the postprocessing, designed the study and wrote the paper.

Acknowledgment

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References

Mid-term follow-up of pulmonary regurgitation by transannular patch


