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ORIGINAL ARTICLE

Cardiac Magnetic Resonance in long term follow-up of Tetralogy of Fallot

Resonancia magnética cardíaca en el seguimiento alejado de pacientes con tetralogía de Fallot

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Abstract

Introduction: Tetralogy of Fallot (TOF) is the most frequent cyanotic congenital heart disease. Pulmonary regurgitation (PR) and right ventricle (RV) enlargement and dysfunction are the most common long-term complications. Cardiac magnetic resonance (CMR) is the gold standard for RV evaluation. **Objective:** To analyze CMR results in the follow-up of TOF patients. **Patients and Method:** All CMR performed between 2007 and 2012 in TOF patients with transannular patch (TAP) repair or infundibular widening, and without pulmonary valve replacement (PVR) were included. Pulmonary regurgitant fraction (PRF), ventricular end-diastolic (EDV) and end-systolic volume (ESV), and ejection fraction (EF) were examined. **Results:** 122 CMR were performed in 114 patients. Average age at CMR was 15.4±7.4 years. 53.3% of them presented severe PR (> 40%). RVEDV was 157.3 ± 38.6 ml/m^2, RVESV was 85.3 ± 27 ml/m^2 and RVEF was 46.4 ± 7.1%. RVEDV was > 150 ml/m^2 in 48.4% and > 170 ml/m^2 in 32.8% of patients. Patients with TAP showed larger RV volumes compared with those with infundibular widening. RVEDV > 170 ml/m^2 showed worse RVEF that those with lower RVEDV (47.9 ± 7% vs 43.2 ± 6.4%, p < 0.01). **Conclusion:** Almost half of the patients showed significant RV enlargement, demonstrating that the indication of CMR is late in their follow-up. TAP was associated with higher RVEDV and RVESV, but no worse RVEF.

Keywords:
Tetralogy of Fallot; pulmonary regurgitation; end-diastolic volumes; transannular patch; cardiac magnetic resonance

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Introduction

Tetralogy of Fallot (ToF) is the most frequent cyanotic congenital heart disease (CHD), with an incidence ranging from 7% to 10% of all CHD. It has an incidence of 0.28 for every 1,000 live birth and an equal proportion of males and females[1]. Etienne-Louis Arthur Fallot first reported it in 1888 as the association of a malaligned ventricular septal defect (VSD), overriding of the aorta over the interventricular septum, obstruction of the right ventricular outflow tract (RVOT) and right ventricular hypertrophy (RVH)[2]. In 1970, Van Praagh described it for the first time as a 'monology', mainly due to the under-development of the pulmonary infundibulum, secondary to the anterior and cephalic displacement of the infundibular septum[3].

The surgical treatment consists of the closure of the VSD and relief of the RVOT obstruction; when the pulmonary annulus is considered hypoplastic, it can be necessary the use of a transannular patch (TAP)[4]. In some cases, when the pulmonary annulus is of adequate size, resection of muscle at the infundibular level is enough. Currently, complete surgical repair is the standard treatment for this pathology, with surgical mortality ranging from 0.9 to 7.5%, depending on the series and type of reparation[4]. It is common to find malfunction of the pulmonary valve during long-term follow-up, due to either regurgitation, stenosis or a combination of both, which is associated with volume overload and/or pressure overload of the right ventricle (RV) and its posterior dilatation and/or progressive dysfunction, arrhythmia and/or sudden death[5]. RV evaluation through echocardiography is difficult, especially under postsurgical conditions. Nowadays, magnetic resonance imaging (MRI) is considered the gold standard in the anatomical and functional evaluation of the RV. This test has become an essential tool in the decision making process aimed to decide the best moment to perform a pulmonary valve replacement (PVR) in these patients[6].

The main objective of this study is to perform a descriptive analysis of the anatomical and functional information obtained by MRI in the follow-up of repaired ToF patients in our center. This descriptive analysis aims to the following: (1) to characterize patients with ToF referred to MRI, specifically their previous status to PVR and (2) to compare characteristics of RV and LV in patients repaired with different surgical techniques. Our hypothesis is that the analyzed population will show a significant dilatation of the RV and patients with TAP will show greater dilatation and worse RV ejection fraction (RVEF) than patients who underwent an infundibular resection. With this study, we expect to characterize this population, as well as a contribution in decision making in the referral to MRI and the timing for PVR.

Methods

All MRI studies performed to patients with repaired ToF, at the Radiology Service of the Clinical Hospital of Pontifical Catholic University of Chile, between January 2007 and June 2012, were analyzed retrospectively. Patients repaired with TAP and infundibular resection techniques, which had not undergone PVR, were included. Patients repaired with RV to pulmonary artery conduit were excluded.

The tests were performed by a 1.5 Tesla Siemens magnet (Magnetom Avanto Model). A single expert radiologist in MRI of CHD was present in every test. Each test was programmed individually, according to the identified anatomy. Axial, sagittal and coronal series were performed, as well as cine gradient in multiple planes, flow measurements by phase contrast in proximal aorta, main pulmonary artery (MPA), right and left pulmonary arteries, T1 weighted slices, angioresonance, perfusion studies and late gadolinium enhancement (LGE), this one 10 to 15 minutes after the administration of gadolinium 0.2 mmol/kg.

Cine sequences, T1, angioresonance, perfusion, and LGE series were acquired in apnea in most of the patients, either voluntarily or with anesthesia, depending on age. Flow measures were acquired in free breathing. Once the images were acquired, the analysis at the workstation was performed by the same radiologist.

The demographic variables of the studied population were analyzed, such as gender, age at the surgical repair, technique of surgical repair and age at the time of the test. From the information obtained from MRI, variables such as volume and function of both ventricles, valve function and characteristic of the heart chambers and great vessels (aortic root and pulmonary arteries) were analyzed. Volume of flow at pulmonary arteries and differential pulmonary flow were evaluated.

Descriptive statistical analysis of the study was presented as average ± standard deviation in the case of continuous variables and as percentages for categorical variables. Comparative analysis of groups was performed with t-student test in the case of continuous variables and with chi-square in the cases of categorical variables, accordingly. A p value < 0.05 was defined as statistically significant.

Results

A total of 122 MRI were performed in 114 patients who met the inclusion criteria, 59% were males.

Mean age at the time of surgical repair was 12.2 months (ranging from 2 to 27 months). A 77.7% of the patients underwent repair with TAP technique and 22.3% were repaired with infundibular resection, sparing the pulmonary valve.

Mean age at MRI was 15.4 ± 7.4 years, with a mean time interval between surgical repair and MRI of 13.3 ± 5.8 years.

General characteristics of patients and MRI data (volumes and ventricular function measurements) are described in Table 1.

The average pulmonary regurgitant fraction (PRF) was 39.9% ± 13.1% in the MPA; 31.2% ± 14.1% in the right pulmonary artery (RPA) and 40.7% ± 17.1% in the left pulmonary artery (LPA). Eighty-eight percent of patients had pulmonary regurgitation (PR) with PRF ≥ 25% (moderate) and 53.3% PRF ≥ 40% (severe). Regarding net differential pulmonary blood flow, it was 61.5% ± 11% to the RPA and 38.5% ± 11% to the LPA.

Regarding RV measurements, mean end-diastolic volume (RVEDV) was 157.3 ± 38.6 cc/m^2 and end-systolic volume (RVESV) was 85.3 ± 27 cc/m^2. A 48.4% of patients showed an RVEDV > 150 ml/m^2 and 32.8% of the patients showed RVEDV > 170 ml/m^2. Furthermore, 33.6% showed an RVESV > 80 ml/m^2. In the LV, the mean LVEDV was 78.0 ± 14 cc/m^2 and LVESV 34.6 ± 9.5 cc/m^2.

Regarding ventricular function, the average RVEF was 46.4 ± 7.1% and LVEF was 55.8 ± 7.6%. From the total of studied patients, 43.7% had RV systolic dysfunction, defined as RVEF lower than 45%, and 35.2% had LV systolic dysfunction, defined as LVEF lower than 55%.

After analyzing by groups, according to surgical technique, it was observed that patients repaired with TAP presented RVEDV and RVESV significantly higher than those repaired with infundibular resection. However, no significant differences were found in RV or LV systolic function nor in LV volumes (Table 2).

When analyzing patients according to RVEDV, it was observed that those patients with RVEDV > 170 ml/m^2 had a significantly lower RV systolic function. This group also presented a significant higher LVEDV and LVESV. However, there was no significant difference of LVEF, according to RVEDV (Table 3).

The aortic size showed a mean Z value of +3.2 ± 1.7 at the annulus; +2.4 ± 1.2 at the sinus of Valsalva and +2.1 ± 1.6 at proximal ascending aorta. 52% of the patients presented aortic root dilatation, defined as a Z value > +2 in any of its portions. Also, 28.7% of the patients had a right aortic arch.

Discussion

Most of the ToF patients who underwent surgical repair present long-term postoperative complications,

Table 1. General characteristics of patients and cardiac magnetic resonance data (mean ± standard deviation)

	Mean ± SD
Age (years)	15.4 ± 7.4
Body surface area (m^2)	1.38 ± 0.37
Time after surgical repair (years)	13.3 ± 5.8
RVEDV (ml/m^2)	157.3 ± 38.6
RVESV (ml/m^2)	85.3 ± 27
RVEF (%)	46.4 ± 7.1
LVEDV (ml/m^2)	78.0 ± 14
LVESV (ml/m^2)	34.6 ± 9.5
LVEF (%)	55.8 ± 7.6
Pulmonary RF (%)	39.9 ± 13.1

SD: standard deviation. EDV: end-diastolic volumen. ESV: end-systolic volume. EF: ejection fraction RV: right ventricular. LV: left ventricular. RF: regurgitant fraction.

Table 2. Right and left ventricular volumes depending on surgical technique (mean ± standard deviation)

	Transannular patch	Pulmonary valve-sparing repair	
RVEDV (ml/m^2)	165.6 ± 39.5	133.6 ± 30.7	p < 0.01
RVESV (ml/m^2)	90 ± 27.7	73.3 ± 24.8	p < 0.02
RVEF (%)	46.4 ± 7	45.9 ± 7.5	p: 0.78
LVEDV (ml/m^2)	78.8 ± 13.7	77.3 ± 14.3	p: 0.67
LVESV (ml/m^2)	35 ± 8.36	33.7 ± 9	p: 0.6
LVEF (%)	55.8 ± 6.8	56.5 ± 6.9	p: 0.68

EDV: end-diastolic volumen. ESV: end-systolic volume. EF: ejection fraction RV: right ventricular. LV: left ventricular. RF: regurgitant fraction.

Table 3. Right and left ventricular characteristics depending on RVEDV (mean ± standard deviation)

	RVEDV ≤ 170 ml/m^2	RVEDV > 170 ml/m^2	
RVEF (%)	47.9 ± 7	43.2 ± 6.4	p < 0.01
LVEDV (ml/m^2)	74.7 ± 12	84.8 ± 15	p < 0.01
LVESV (ml/m^2)	32.7 ± 9.5	38.6 ± 8.3	p < 0.01
LVEF (%)	56.5 ± 8.3	54.5 ± 5.8	p: 0.13

EDV: end-diastolic volumen. ESV: end-systolic volume. EF: ejection fraction RV: right ventricular. LV: left ventricular.

including various degrees of residual PR, which is present in almost every repaired patient. This leads to a progressive dilatation of the RV with possible risk of dysfunction. Although these alterations are usually well tolerated during childhood and adolescence, the incidence of arrhythmias, deterioration of the functional capacity, heart failure and sudden death are tripled during the third postoperative decade. Thus, it is essential to establish a long-term follow-up protocol.

Among the available tests, MRI is the best imaging technique to evaluate morphological and functional anomalies in ToF patients at late follow-up, mainly because it has no window limitation and it is not affected by ventricular geometry, due to its tridimensional and multiplane capacity. Therefore, it allows to evaluate ventricle dimensions and function, without assuming a geometry of the heart chambers; it also provides quantitative data, such as heart chambers volumes and blood flow patterns, including valve RF, and systolic and diastolic ventricular function estimation. It also allows tissue characterization, with LGE study, that can detect the presence of fibrosis and ischemic scars due to coronary lesions, which are a potential cause of arrhythmias. This is important in long-term follow-up, where the consequences of PR in the RV are evaluated in order to decide the best timing for PVR[7]. A recent study determines that an interval of approximately three years between the first MRI and the next follow-up study has the best balance between sensitivity and specificity (63% and 64%, respectively) for the detection of disease progression, defined as an increase of RVEDV ≥ 30 ml/m^2, a decrease of RVEF ≥ 10% or a decrease of LVEF ≥ 10%. However, this must be validated by future studies[8]. MRI is also useful to evaluate the result of PVR in terms of ventricular remodeling and in the evaluation of prosthesis dysfunction in posterior follow-up.

In this study, it is observed that those patients with ToF referred to our center for their first follow-up MRI have an average age of 15,4 ± 7,4 years. Almost half of them have a significant dilatation of the RV; 53.3% have severe PR; 43.7% have RV systolic dysfunction and 35.2% have LV systolic dysfunction. When considering all this data, and taking into account the proposed and summarized criteria by Tal Geva for PVR in patients with ToF[6], (Evidence grade C), such as the presence of RVEDV > 150 ml/m^2, RVESV > 80 ml/m^2, RV systolic dysfunction and/or LV systolic dysfunction, among others, in patients with at least moderate PR, and considering clinical symptoms, it is possible to conclude that in our series, at least half of the referred patients who required MRI had already PVR indication.

More recent studies demonstrated that significant power loss is present in ToF patients with PR and that RV efficiency and power capacity diminishes exponentially as the RV volume increases[10], with curve flattening observed with RVEDV > 139 ml/m^2 and RVESV > 75 ml/m^2. Therefore, according to this study, almost two thirds of our patients referred to MRI would present a deterioration in RV efficacy and potency.

In addition, approximately one-third of the patients already had an RVEDV > 170 ml/m^2 and RVESV > 80 ml/m^2. Studies based on MRI performed in patients with ToF demonstrated that in those patients with RVEDV > 160 to 170 ml/m^2 or with RVESV > 80 to 85 ml/m^2, it is less likely the complete RV remodeling after PVR[11-13]. In our series, it was observed that patients with RVEDV > 170 ml/m^2 had significantly worse RV systolic function, as well as higher LVEDV and LVESV than patients with lower RV volumes. According to this, in about one-third of patients, the request for this test would have been late.

It has been reported that severe RV dilatation and especially RV and LV systolic dysfunction, are independent risk factors for worse clinical status or lower functional capacity, the onset of arrhythmias and death[14-16]. In our study, there was no significant difference in the LVEF of patients with a higher RVEDV and/or worse RVEF. This can be explained by the age of the studied population and for the lack of consecutive follow-up of these patients through an MRI, which can allow evaluating LVEF serially and potential deterioration in relation to the progression of RV deterioration.

Analyzing the results according to surgical technique, it was observed that patients repaired with TAP had more RV dilatation on the long-term follow-up than those patients repaired with infundibular resection. This finding has been described by some studies where the TAP was identified as a risk factor for RV progressive dilatation[17] (OR 2.956 - IC 95%: 1.073 – 8.138) or where it shows that repair performed with TAP had a higher risk of further surgery but without affecting the mortality of these patients[18-19]. The association between infundibular resection and TAP and the higher RV dilatation is probably explained in the study by Puranik et al.[20] where it was observed that in those patients that underwent surgical repair with TAP, the RVOT was considered as contractile in only 50% of patients and this would be responsible for the higher ESV and worse global systolic function of both ventricles. This finding suggests that the referral for MRI should be performed earlier in these patients in order to define the adequate timing to perform PVR and to preserve or recover the function and/or morphology of the dilated RV. However, in our study, there was no statistically significant difference in relation to systolic function of both ventricles and LV dilatation when comparing both surgical techniques. The possible explanations are: first, the different age at repair between these studies (12.8 months versus 2.8 years), thus a probable smaller TAP in our patients, and second, the different age at the time of the MRI (15.4 ± 7.4 years versus 25.1 ± 1.2 years), which means that our patients had experienced fewer years of PR and/or RV dilatation at the time of MRI.

Regarding the aorta, it was observed that more than half of the studied patients had aortic root dilatation[21]. This finding was already reported previously, in a similar proportion, but in studies performed exclusively in adults[22,23]. In these reviews, it was observed that the aortic root dilatation is a risk factor for developing aortic valve insufficiency, where a valve or aortic root replacement is sometimes needed.

MRI is the method of choice for evaluation of ToF patients in the long-term follow-up, since altogether with clinical and electrocardiographic parameters, would allow to determine the most adequate timing to perform PVR, considering the current recommended criteria, in order to avoid severe RV dilatation, resulting in the progression of function deterioration.

Reports regarding the frequency of MRI evaluation in these patients are limited. On the other hand, it is difficult to determine a universal recommendation due to severity spectrum of the pathology and different surgical techniques, such as the use or not use of TAP, as well as its size, along with many other factors and/or complications of the surgery itself. Thus, we believe that more studies are needed to correlate these factors with progression of dilatation, as well as the functional deterioration of the ventricles, especially the RV. It is essential to incorporate the clinical evaluation, including the functional capacity, as well as other echocardiographic parameters that would allow a better approach to determine the best moment to request an MRI in order to avoid irreversible RV dysfunction.

Our study presents the first characterization with MRI of patients with repaired ToF at long term follow-up in Chile. Limitations of our work are the lack of detailed clinical information that could contribute to the analysis with the information obtained by MRI (functional capacity, ECG characteristics, echocardiogram, extracorporeal circulation and aortic clamping time, etc.), as well as bias inherent to the referral in order to perform this test, being this sample a selected population of patients who were referred for MRI due to their clinical characteristics and/or echocardiogram. However, despite these limitations, our results contribute valuable information in our country and allows us to conclude that MRI is requested relatively late in an important proportion of our patients. An earlier referral to MRI can optimize PVR timing in this population and the final goal to preserve ventricular function.

Ethical responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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