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Original article

Magnetic resonance imaging of the heart as a method of long-term monitoring of right heart function after tetralogy of Fallot surgery

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Summary

Introduction. Cardiac magnetic resonance imaging (CMR) is considered the reference diagnostic method for quantifying right ventricular size and function, and pulmonary regurgitation in patients with tetralogy of Fallot surgery. The aim of this paper is to confirm the importance of magnetic resonance continuous postoperative monitoring of right and left heart function parameters as a diagnostic method that provides the most precise and accurate assessment.

Methods. The prospective observational study included subjects with TOF surgery who were diagnosed with residual morphological and/or functional disorders on control postoperative echocardiographic examinations. All subjects underwent magnetic resonance imaging of the heart on a 1.5 T scanner with dedicated coils for the heart surface according to the standard protocol for a period of one year from the beginning of the study. Criteria for exclusion from the study were: significant residual pulmonary stenosis, condition after pulmonary valve replacement, existence of residual shunt lesions, contraindications for cardiac magnetic resonance imaging (pacemaker, ICD, claustrophobia). Depending on the time elapsed since the tetralogy of Fallot surgery, the subjects were divided into groups: more than 15 years, 11–15 years, 6–10 years, less than 5 years.

Results. The study included 131 subjects with an average age of 24.18 ± 11.57 years with complete correction of TOF. Intergroup differences in values of right ventricular end-diastolic volume, right ventricular ejection fraction, and left ventricular ejection fraction were demonstrated, but there was no statistically significant intergroup difference in values of pulmonary regurgitation fraction. The negative interaction of the right and left ventricles intensifies during the years of follow-up of patients after TOF surgery, which is especially true fifteen years after surgery.

Conclusion. CMR has the most significant role in research efforts aimed at improving the outcomes of operated patients with tetralogy of Fallot.

Key words: tetralogy of Fallot, right ventricular dysfunction, cardiac magnetic resonance imaging

Introduction

In the longitudinal follow-up of patients operated for tetralogy of Fallot, the detection of morphological and hemodynamic residual disorders in asymptomatic and symptomatic patients is of great importance in order to decide on new therapeutic measures, such as pulmonary valve replacement, in order to improve the course and outcome of treatment [1]. Therefore, it

is important to identify risk factors for sudden cardiac death, as well as serious complications such as ventricular tachycardia and heart failure in patients with tetralogy of Fallot (TOF). Improved surgical procedures have reduced early mortality to less than 3%, but the annual mortality rate has multiplied 20–30 years after initial surgical remediation, mainly due to adverse cardiac events.

Pulmonary regurgitation (PR) is the most common complication in patients with TOF surgery, which is associated with progressive dilatation and impaired right ventricular systolic function (RV), and it adversely affects left heart function and geometry due to unfavorable ventriculo-ventricular interaction [5–11]. The ratio of right and left ventricular volume is a significant predictor of PR severity and right and left heart dysfunction [12–14]. Therefore, surgical replacement of the pulmonary valve is associated with a significant reduction in RV volume and an increase in right and left ventricular systolic function, shortening the duration of the QRS complex, improving symptoms, and NYHA functional class [15]. Other residual disorders after TOF surgery include tricuspid regurgitation, dysfunction, aortic root dilatation and ascending aorta, aortic regurgitation, residual atrial and ventricular septal defect, right ventricular outflow tract aneurysm, pulmonary artery branch stenosis.

Rhythm disorders are common in patients operated on for TOF: right-branch block with prolongation of the QRS complex is present in most patients; atrial flutter or fibrillation and ventricular tachycardia do not appear until the third or fourth decade of life. Cardiac magnetic resonance imaging (CMR) is considered a reference diagnostic method for quantifying right ventricular size and function and pulmonary regurgitation in patients with TOF surgery, as it provides a comprehensive accurate assessment of right and left heart morphology and physiology, and contributes to optimal types and times of reintervention [20–22]. The aim of this paper is to confirm the importance of magnetic resonance continuous postoperative monitoring of right and left heart function parameters as a diagnostic method that provides the most precise and accurate assessment.

Methods

The research included respondents with TOF surgery who in the period from 1 January 2012 to 30 September 2016 were diagnosed with residual morphological and/or functional disorders at postoperative control echocardiographic examinations. All subjects underwent magnetic resonance imaging of the heart within a period of one year from the beginning of the study.

Criteria for inclusion in the study were: asymptomatic subjects regardless of age who underwent complete correction of tetralogy of Fallot, and who were diagnosed with pulmonary regurgitation as the leading residual hemodynamic disorder at postoperative control echocardiographic examinations.

Criteria for exclusion from the study were: significant residual pulmonary stenosis, condition after pulmonary valve replacement, existence of residual shunt lesions, contraindications for cardiac magnetic resonance imaging (pacemaker, ICD, claustrophobia).

Depending on the time elapsed since the tetralogy of Fallot surgery, the subjects were divided into groups: more than 15 years, 11–15 years, 6–10 years, less than 5 years. The study was approved by the competent ethics committee.

Subjects underwent cardiovascular magnetic resonance imaging (CMR) according to a standard protocol. Magnetic resonance imaging of the heart was performed on a 1.5 T scanner with dedicated coils for the heart surface. Using two-dimensional high-speed shooting, steady-state acquisition sequences (steady-state free precession) in the short axis

direction were used. Recording parameters were as follows: flip angle 45°, echo time (TE) set to full minutes, repeat time (TR) 3.4–3.6 ms, cross-sectional thickness 8 to 9 mm, spacing 0 to 1 mm, 12 views/ segment, 111 KHz reading bandwidth, rectangular field of view (30–34 cm) and 160 scan matrix. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Pulmonary valve flow measurement was performed perpendicular to the flow using a standard two-dimensional retrospective-sensitized flow sequence. Thirty heart phases were reconstructed retrospectively. The recording parameters were as follows: two-dimensional fast faulty gradient echo, TR 6 to 7 ms, TE 3 ms, rotation angle 20°, reading bandwidth 90 KHz, 6 mm cross-sectional thickness, 6 views/segment, rectangular field of view (75% direction of infusion coding) and a scan matrix of 256 • 128. Recording was performed at rest and after administration of low doses (7.5 μg/kg-1/min-1) and high doses (20 μg/kg-1/min-1) dobutamine. Contraindications to the use of dobutamine were previous persistent ventricular tachycardia (often recurrent), supraventricular tachycardia, and obstruction of ventricular inflow or outflow. Available workstations were used for CMR analyzes. The volumetric data set of the ventricles was quantitatively analyzed using manual delineation of endocardial boundaries in end-systole and end-diastole excluding large trabeculae (visible at the next 3 cross-sections) and papillary muscles from blood volume. Biventricular end-diastolic volume, end-systolic volume, ejection fraction (EF) and valvular regurgitation fraction were calculated and compared with reference values.

The parameters of right ventricular dysfunction analyzed on CMR are: corrected right ventricular ejection fraction (cor RV-EF), regurgitation volume (RVol) and pulmonary regurgitation fraction (PRF).

The parameters of ventriculo-ventricular interaction analyzed on CMR are: the ratio of end-diastolic volumes of the right and left ventricles (RV/LV) and paradoxical movements of the interventricular septum.

Based on the severity of pulmonary insufficiency, i.e. gradation of the pulmonary regurgitation fraction (PRF) diagnosed with CMR, the subjects were divided into groups: mild (PRF <20%), moderate (PRF 21%–40%) and severe (PRF> 41%) regurgitation. The PRF value represents the retrograde-to-anterograde flow ratio on the pulmonary valve expressed as a percentage.

Based on the size of the right ventricle, i.e. RV-EDV (Right ventricle-End diastole volume) the subjects were divided into groups: mild dilatation RV (RV-EDV 110–140 mL/m2), moderate dilatation (RV-EDV 141–170 mL/m2) and severe dilatation (> 170 ml/m2).

Based on the values of the ejection fraction (EF) of the right ventricle, the subjects were divided into two groups: subjects with preserved (RV-EF ≥45%) and reduced ejection fraction (RV-EF <45%).

Statistical analysis of the data was done using the SPSS 24.0 statistical software package. Descriptive data are presented as absolute numbers, frequencies, percentages, average values +/- standard deviations, minimum and maximum values. The χ2-square test or Fisher's test of exact probability was used out of the nonparametric statistical tests, as well as the Mann-Whitney U test for ordinal data. Among the parametric tests, the independent samples t test and one-factor analysis of variance - ANOVA were used. Linear regression or Pearson/Spearman rank correlation was used to investigate the correlation.

Results

The study included 131 subjects with complete TOF correction who were diagnosed with residual hemodynamic and morphological disorders, primarily pulmonary regurgitation, at postoperative control echocardiographic

examinations. 52.7% of respondents were male and 47.3% were female. The mean age of the subjects was 24.18 ± 11.57 years. The group younger than 17 years consisted of 40 respondents (30.5%) with an average age of 12.95 ± 3.27 years. The group older than 17 years consisted of 91 respondents (69.5%) with an average age of 29.12 ± 10.4 years. 36 (27.5%) respondents had mild PRF, 45 of them had moderate PRF (34.4%) and 50 (38.2%) respondents had severe PRF.

Right ventricular dilatation was not found in 59 (45%) respondents, while 43 (32.8%) respondents had mild dilatation, 17 (13%) respondents had moderate dilatation, and 12 (9.2%) had severe dilatation of the right ventricle.

Preserved ejection fraction of the right ventricle was found in 100 (76.3%) respondents, while 31 (23.7%) respondents had reduced EF-RV. TOF surgery was performed more than 15 years ago in 72 (55%) subjects, 11–15 years ago in 35 (26.7%), 6–10 years ago in 17 (13%) respondents, while 7 (5.3%) of respondents were operated on in the last 5 years.

One-factor analysis of variance - ANOVA examined the dependence of the time elapsed on TOF surgery (less than 5 years, 6–10 years, 11–15 years, more than 15 years) and end-diastolic volume of the right ventricle. A high statistically significant difference was observed between the examined groups ($F = 4.105$, $p = 0.008$) (Table 1).

A statistically significant difference in the mean values of the ejection fraction of the right ventricle was observed between the group of subjects who had surgery less than 5 years ago and the group of subjects who had surgery 6–10 years ago, and between the group of subjects who had surgery 6–10 years ago and the group of subjects who had surgery 11–15 years ago. A high statistically significant difference ($p = 0.001$) was also observed between the group who were operated on 6–10 years ago and the group who were operated on more than 15 years ago. The obtained results are shown in Table 1.

A high statistically significant difference ($p = 0.001$) in the mean values of the ejection fraction of the left ventricle was observed between the group of subjects who underwent the surgery 6–10 years ago and the group of subjects who underwent the surgery 11–15 years ago. A high statistically significant difference ($p = 0.004$) was also observed between the group who underwent the surgery 11–15 years ago and the group who underwent the surgery more than 15 years ago. The results are shown in Table 1.

No statistically significant differences in the mean values of the pulmonary regurgitation fraction were observed between the groups of subjects divided on the basis of the time period from the operation (Table 1).

No statistically significant differences in the mean values of end-diastolic volume of the right and left ventricles were observed between the groups of subjects divided on the basis of the time period from the operation (Table 1).

No statistically significant differences in the mean values of the corrected ejection fraction of the right ventricle were observed between the groups of subjects divided on the basis of the time period from the operation (Table 1).

Linear regression showed that the EDV-RV/EDV-LV ratio has a higher beta coefficient ($\beta = 0.461$) and is a statistically significant ($p = 0.001$) predictor of the severity of pulmonary regurgitation compared to RV-EDV ($\beta = 0.047$, $p = 0.711$).

Discussion

The study included 131 subjects with an average age of 24.18 ± 11.57 years with complete correction of TOF who were diagnosed with residual hemodynamic and morphological disorders, primarily pulmonary regurgitation, on postoperative echocardiographic examinations.

Table 1. Statistical analysis of parameters of ventricular (dys)function on CMR

Parameter of ventricular (dys)function on CMR (SV ± SD)		F ip (between groups)		p (within groups)	
		F	p	Time elapsed from surgery	p
End-diastolic volume of the right ventricle (ml/ m2)					
<5 years				6–10 years	0.883
6–10 years	86.31 ± 28.48			11–15 years	0.470
11–15 years	99.01 ± 30.36			<5 years	0.263
> 15 years	115.50 ± 26.42	4.105	0.008	<5 years	0.048
6–10 years	126.20 ± 45.09			> 15 years	0.048
11–15 years				> 15 years	0.553
Right ventricular ejection fraction (%)					
<5 years				6–10 years	0.599
6–10 years	59.98 ± 8.64			11–15 years	0.986
11–15 years	55.94 ± 7.76			<5 years	0.383
> 15 years	55.20 ± 6.78	13.215	0.001	<5 years	0.001
6–10 years	48.25 ± 7.17			> 15 years	0.001
11–15 years				> 15 years	0.001
Left ventricular ejection fraction (%)					
<5 years				6–10 years	0.998
6–10 years	66.11 ± 7.85			11–15 years	0.656
11–15 years	66.65 ± 5.80			<5 years	0.919
> 15 years	64.22 ± 3.81	8.119	0.001	<5 years	0.071
6–10 years	59.17 ± 8.41			> 15 years	0.001
11–15 years				> 15 years	0.004
Pulmonary regurgitation fraction (%)					
<5 years				6–10 years	0.991
6–10 years	28.64 ± 13.54			11–15 years	0.884
11–15 years	31.00 ± 13.74			<5 years	0.831
> 15 years	34.80 ± 18.43	0.347	0.791	<5 years	0.944
6–10 years	32.53 ± 18.14			> 15 years	0.988
11–15 years				> 15 years	0.923
The ratio of end-diastolic volume of the right and left ventricles					
<5 years				6–10 years	0.999
6–10 years				11–15 years	0.842
11–15 years	1.45 ± 0.35			<5 years	0.892
> 15 years	1.47 ± 0.26	20.814	0.488	<5 years	0.739
6–10 years	1.61 ± 0.36			> 15 years	0.561
11–15 years	1.67 ± 0.68			> 15 years	0.953
Corrected right ventricular ejection fraction (%)					
<5 years				6–10 years	0.667
6–10 years	43.40 ± 13.30			11–15 years	0.882
11–15 years	37.81 ± 9.53	2,295	0.081	<5 years	0.297
> 15 years	35.42 ± 9.64			<5 years	0.100
6–10 years	33.38 ± 11.58			> 15 years	0.439
11–15 years				> 15 years	0.901

Surgical replacement of the pulmonary valve has been associated with a significant reduction in RV volume and an increase in right and left ventricular systolic function, shortening the duration of the QRS complex, improving symptoms, and NYHA functional class [15]. The ratio of right and left ventricular volume is a significant predictor of PR severity and right and left heart dysfunction [12–14]. As a relative indication for the replacement of the pulmonary valve, as in other congenital heart diseases, effort intolerance can be taken, i.e. reduced exercise capacity, but outcomes may be better if surgery is performed before the heart is dilated and before clinical status deteriorates [23].

In patients with symptoms of exercise intolerance, improvement in symptoms may be expected after pulmonary valve replacement, but no improvement in formal exercise testing parameters has yet been confirmed. In early childhood to the second decade of life, pulmonary regurgitation is well tolerated, and from the second decade of life it is associated with an increased risk of death due to ventricular arteries [23–26].

In order to determine the optimal time for lung valve replacement, a number of papers have analyzed preoperative RV volume limit values above which there is no postoperative reduction or normalization of RV size.

Villafañe et al. in their work published a "cut-off" value of 160 ml/m2 for normalization of RV end-diastolic volume and 82 ml/m2 for RV end-systolic volume [27].

Geva et al. in her study (multivariate cohort analysis) identified a preoperative RV-ESV index <90 ml/m2 and a QRS duration <140 ms, which would be associated with an optimal postoperative outcome (normal RV size and function), and an RV-EF <45% and QRS ≥160 ms were associated with suboptimal postoperative outcome (RV dilatation and dysfunction) [3, 4, 20].

Indications for any surgical intervention exist when the benefits outweigh the risks and when reinterventions can positively change the course of the disease. Indications for pulmonary valve replacement (PVR) can potentially include objective indications such as reduced mortality. Other acceptable indications would include alleviation of symptoms and improvement of quality of life [24, 25, 28].

In our study of 131 subjects, 76.3% of subjects had a preserved right ventricular ejection fraction, while 23.7% of subjects had reduced EF-RV.

Severe pulmonary regurgitation (PR) is usually associated with a regurgitation fraction of over 40%, which is generally well tolerated over a long period of time. However, PR worsens under conditions of increased pulmonary artery pressure, e.g. in pulmonary artery branch stenosis, acquired bronchopulmonary disease, left ventricular dysfunction, or pulmonary vascular disease. The adaptive RV response to the volume of load resulting from PR depends not only on the degree and duration of pulmonary regurgitation, but also on the characteristics of the right ventricle and pulmonary arteries. The volume load of the right ventricle causes an increase in EDV-RV, but with time also an increase in ESV-RV, which leads to a progressive deterioration of myocardial function. In adulthood, poor adaptation of the hypertrophied and noncompliant right ventricle to excessive volume load of significant PR leads to progressive deterioration and dysfunction of the right heart.

The time period elapsed from the operation to our research for the largest number of our respondents was longer than 15 years (45%), and the smallest number of our respondents was operated on in a period shorter than 5 years. This is explained by the fact that CMR examination is rarely performed in children in the relatively early postoperative period (up to 5 years), and when it is performed it means that there are significant sequelae after surgery. For this reason, this group of children is not similar to other age groups. One-way analysis of variance - ANOVA examined the influence of time elapsed since

TOF surgery (less than 5 years, 6–10 years, 11–15 years, more than 15 years) and end-diastolic volume of the right ventricle, as a parameter of size and global RV function. A high statistically significant difference was observed between the examined groups ($F = 4.105$, $p = 0.008$). This indicates the fact that EDV-RV worsens during the years of follow-up, especially 15 years after the surgery. Based on this, it can be concluded that more frequent controls and adherence to the algorithm of diagnostic procedures in the time after surgery, including cardiac magnetic resonance imaging, are needed, especially for subjects who underwent surgery 15 years ago [29].

Statistical analysis of the data showed intergroup differences in the values of the ejection fraction of the right ventricle and the ejection fraction of the left ventricle, but there was no statistically significant intergroup difference in the values of the fraction of pulmonary regurgitation.

As no statistically significant differences in mean PRF values were observed between groups of subjects divided by the time period elapsed from surgery, special caution should be exercised in routine follow-up EHO examinations during postoperative evaluation, as it may give the false impression that the disease is stagnant, and the condition is actually becoming worse and leads to global heart failure.

No statistically significant differences in the mean values of end-diastolic volume of the right and left ventricles, nor in the mean values of the corrected ejection fraction of the right ventricle were observed between the groups of subjects divided on the basis of the time period elapsed from the surgery. Linear regression showed that the EDV-RV / EDV-LV ratio has a higher beta coefficient ($\beta = 0.461$) and is a statistically more significant ($p = 0.001$) predictor of the severity of pulmonary regurgitation compared to RV-EDV ($\beta = 0.047$; $p = 0.711$).

Conclusion

By analyzing the elapsed time period from TOF surgery (less than 5 years, 6–10 years, 11–15 years, more than 15 years), intergroup differences in the values of right ventricular end-diastolic volume, right ventricular ejection fraction, and left ventricular ejection fraction were proven, but there was no statistically significant intergroup difference in the value of the pulmonary regurgitation fraction.

The negative interaction of the right and left ventricles intensifies during the years of follow-up of patients after TOF surgery, which is especially true fifteen years after surgery.

CMR is a key diagnostic method in a growing population of patients operated on for TOF, or the most significant role in research efforts aimed at improving the outcome of patients with tetralogy of Fallot.

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Ethical approval. The Ethics Committee of the Department of Cardiology of the University Children's Clinic (UDK) in Belgrade and the University Hospital (UB) Foca approved the study and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

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Magnetna rezonanca srca kao metod dugoročnog praćenja funkcije desnog srca nakon operacije tetralogije Fallot

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Uvod. Magnetna rezonanca srca (engl. Cardiac magnetic resonance - CMR) se smatra referentnom dijagnostičkom metodom za kvantifikaciju veličine i funkcije desne komore i pulmonalne regurgitacije kod pacijenata sa operisanom tetralogijom Fallot. Cilj ovog rada je da potvrdi važnost magnetno-rezonantnog kontinuiranog postoperativnog praćenja parametara funkcije desnog i lijevog srca kao dijagnostičke metode koja pruža najpreciznu i najtačniju procjenu.

Metode. Opservaciono-prospektivna studija uključila je ispitanike sa operisanom TOF kojima su na kontrolnim postoperativnim ehokardiografskim pregledima utvrđeni rezidualni morfološki i/ili funkcionalni poremećaji. Svim ispitanicima je urađena magnetna rezonanca srca na skeneru jačine 1.5 T sa namjenskim zavojnicama za srčanu površinu prema standardnom protokolu u periodu od godinu dana od početka istraživanja. Kriterijumi za isključenje iz studije bili su: značajna rezidualna pulmonalna stenoza, stanje poslije zamjene pulmonalne valvule, postojanje rezidualnih šant lezija; kontraindikacije za magnetnu rezonancu srca (pace-maker, ICD, klaustrofobija). U zavisnosti od vremena proteklog od operacije tetralogije Fallot, ispitanici su podijeljeni u grupe: više od 15 godina, 11–15 godina, 6–10 godina, manje od 5 godina.

Rezultati. Studijom je obuhvaćen 131 ispitanik prosječne starosti 24,18 ± 11,57 godina sa urađenom kompletnom korekcijom TOF. Dokazane međugrupne razlike u vrijednostima end-dijastolnog volumena desne komore, ejekcione frakcije desne komore, kao i ejekcione frakcije lijeve komore, ali nije bilo statistički značajne međugrupne razlike u vrijednosti frakcije pulmonalne regurgitacije. Negativna interreakcija desne i lijeve komore pojačava se u toku godina praćenja pacijenata nakon operacije TOF, što se posebno događa 15 godina nakon operacije.

Zaključak. CMR ima najznačajniju ulogu u istraživačkim naporima usmjerenim na poboljšanje ishoda operisanih pacijenata sa tetralogijom Fallot.

Ključne riječi: tetralogija Fallot, disfunkcija desne komore, magnetna rezonanca srca