Optimal timing of pulmonary valve replacement in tetralogy of Fallot

Straten, A. van

3

Serial Assessment of Pulmonary Regurgitation and Right Ventricular Function in Tetralogy of Fallot: Time Course Depending on Surgical Technique

A van Straten

T Oosterhof

HW Vliegen

BJM Mulder

MG Hazekamp

A de Roos

JACC submitted

Abstract

Background

Initial surgery of tetralogy for Fallot may involve myectomy / valvulotomy (M / V), right ventricular patch (RVP) repair, or transannular patch (TAP) repair. Variable degrees of pulmonary regurgitation (PR) and consequently right ventricular (RV) dilatation may occur depending on the surgical approach. Limited information is available on the natural course of RV function. The goal of this study is to assess serial changes in PR and RV volumes and function and the time course in relationship to the surgical technique.

Methods

Between January 1990 and May 2005, 97 TOF patients underwent 1 and 45 patients underwent 2 or more cardiac MR examinations. The degree of PR and RV volumes was assessed using standard MRI techniques. Patients were divided into 3 groups based on the type of initial repair: M / V (n=41), RVP repair (n=23), or TAP repair (n=78).

Results

TAP was associated with the highest degree of PR (41 ± 15% vs. 32 ± 17% and 20 ± 17%, respectively in the RVP and M / V groups, P<0.01) and consequently more RV dilatation at baseline (158 ± 45 ml/m^2 vs. 147 ± 40 ml/m^2 and 124 ± 22 ml/m^2, P<0.01). In the TAP group, indexed right ventricular end-diastolic volume (RV-EDV-I) increased by 2.2 ml/m^2 per year (p<0.01) and right ventricular ejection fraction (RV-EF) decreased by 0.37% per year (p=0.01), while no significant change in RV volume and function was found in the other groups, indicating differential patterns of RV function deterioration over time in different types of initial surgery. The degree of PR remained unchanged over time in all 3 groups. Patients in the TAP and RVP group more often underwent pulmonary valve replacement as compared to patients in the M / V group (hazard ratio 2.2, P=0.015).

Conclusion

The degree of PR and RV dilatation is dependent on the surgical technique for TOF correction. TAP is associated with more severe PR and deteriorating RV dilatation with a consequently higher rate of PVR.

Introduction

Surgical repair of Tetralogy of Fallot (TOF) is nowadays preferably performed in the first year of life as it allows for a one step approach without the need for a prior palliative aortic-pulmonary shunt. Further benefits include the improved development of the pulmonary vascular bed and the reduced pressure on the right ventricle, diminishing the development of right ventricular hypertrophy [1].

However, these benefits have to be weighed against the inevitably higher rate of the need for a trans-annular patch (TAP) in the neonate leading to late pulmonary regurgitation (PR) [2]. Other types of initial repair, associated with less PR as compared to the TAP procedure, include the use of a patch confined to the right ventricular outflow tract (RVP) and myectomy with or without valvulotomy (M / V). It was long thought that mild to moderate PR was rather harmless, however, in recent years evidence of the deleterious effects of longstanding PR has become available. It is now well recognized that PR is associated with right ventricular (RV) enlargement, late arrhythmias and it may reduce exercise capacity [3,4]. In patients with severe PR and/or RV enlargement pulmonary valve replacement (PVR) is often performed to reduce the RV volume and consequently reducing the risk for the development of severe arrhythmias. Previous studies have shown the beneficial effects of PVR on RV volumes and function [5-7], however, optimal timing of PVR remains uncertain as the long term effects of PVR and the need for re-operations are not completely understood, although recent studies have shown that right ventricles with an end-diastolic volume of more than 160 – 170 ml/m^2 may not normalize following PVR [8,9].

Since the type of initial surgery is the main determinant for the degree of late PR, differential patterns for RV function deterioration may be seen in the long-term follow-up of repaired TOF patients. Previous studies on the time course of cardiac function in patients with TOF used echocardiography or clinical parameters to assess cardiac function [10,11]. Nowadays cardiac MRI is the gold standard for assessment of cardiac function because of its ability to quantify flow and ventricular volumes with high accuracy and reproducibility.

The purpose of the present study was to assess RV volumes and function using cardiac MRI as well as the time course of RV function deterioration in repaired TOF patients after different types of initial repair in infancy.

Methods

Study group

Between January 1990 and May 2005 163 TOF patients without PVR underwent at least one cardiac MRI. Patients were at least 17 years of age at the time of the first MRI and had no contraindications for MRI. Patients were divided in 3 groups based on the type of total repair in infancy (table 3.1). The typical operations include M / V, RVP and TAP (figure 3.1). Twenty-one patients were excluded because the type of initial repair could not be retrieved from their medical records.

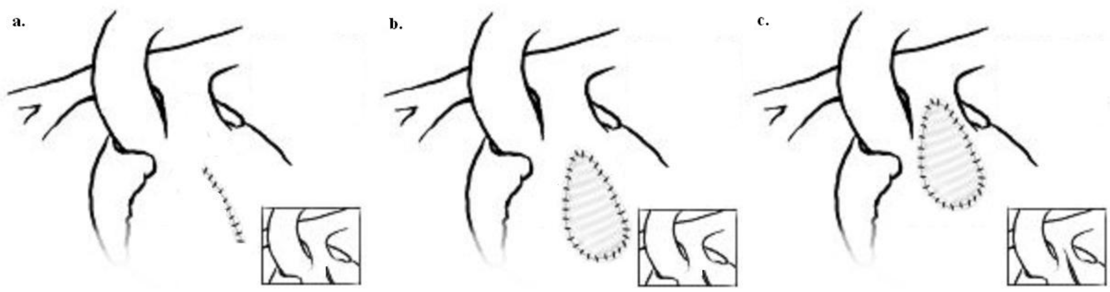

Figure 3.1. *The three different types of initial repair. (A) Direct closure of the right ventriculotomy with or without valvulotomy. (B) Closure of the right ventriculotomy with a patch, and (C) Closure of the right ventriculotomy extending through the pulmonary annulus with a transannular patch.*
Modified after Stephen H. McKellar. © 2003 Cardiothoracic Surgery Network.

Magnetic Resonance Imaging

MRI studies were performed with a 1.5 Tesla system (NT15 Gyroscan, Philips Medical Systems, Best, the Netherlands), according to our clinical protocol, as described previously [5]. In summary, a multiphase, electrocardiogram triggered, multishot echoplanar gradient echo technique was used to acquire short axis images. Images were obtained during breath holds lasting 10 to 15 seconds. Ventricular volumes were calculated by summation of ventricular cavity areas, assessed by manual tracing of the endocardial border on a stack of gradient echo image sections of a specific time frame, and multiplied by section thickness. Papillary muscles and the moderator band were not included in the ventricular area.

Velocity mapping was performed with the use of a velocity-encoded phase contrast sequence, as described previously. Pulmonary flow measurements were performed halfway between the pulmonary valve and the bifurcation or approximately 2 cm proximal to the bifurcation when no pulmonary valve was present. With the use of retrospective gating, 30 to 40 time frames evenly distributed over the cardiac cycle were constructed, resulting in a temporal resolution of 25-35 msec. A 128 x 128 matrix was interpolated to a display matrix of 256 x 256. The examinations lasted 45 to 60 minutes and no sedation was used.

Post-processing

The MR images and velocity maps were analyzed on a remote workstation. The short-axis acquisitions were used to assess biventricular dimensions and ejection fraction. The endocardial and papillary muscle borders of the end-diastolic and end-systolic images from each short-axis slice were manually traced using validated MR analytical software system and the right ventricular end-diastolic volume index (RV-EDV-I) was calculated and right ventricular ejection fraction (RV-EF) were calculated as described before [12,13]. Right ventricular volumes were indexed for body surface area (BSA).

The FLOW analytical software package was used to analyze the velocity maps [12]. A region of interest was manually traced along the inner borders of the pulmonary artery wall in each time frame during the cardiac cycle. For every time frame, spatial averages and spatial maximum flow velocity within the region of interest were automatically measured by a computer algorithm. The instantaneous volume flow was calculated by multiplying the region of interest area and spatial average flow velocity. Pulmonary regurgitant fraction was calculated by the formula: (regurgitant flow / systolic forward flow) * 100.

Statistical Analysis

The SPSS for Windows Software (version 12.0, SPSS, Chicago, Illinois) was used for data analysis. Data are expressed as frequency, mean with standard deviation, or median with range. Chi-squared testing, one-way ANOVA with post-hoc Bonferroni correction, and Kruskal-Wallis testing, was used to analyze differences between the types of initial correction. Independent predictors for baseline MR parameters were analyzed with linear regression analysis. Only parameters that were significantly associated in univariate analysis were selected in the multivariate model. Comparisons between the subsequent MR studies were performed with a linear mixed model analysis with the MR parameter as dependent variable and the following independent variables: type of initial surgery (M / V, RVP and TAP), time after initial correction (years) and their interaction as fixed effects and patient as random effect.

Results

Table 3.1. *Patient characteristics.*

	Type of initial repair (n=142)		
Variable	**RV myectomy / valvulotomy (n=41)**	**RV patch (n=23)**	**Transannular patch (n=78)**
Male/female	17/24	12/11	48/30
Shunt procedure	58%	60%	55%
Age at initial repair (years)	6.1 (0.8-39)	5.7 (1.3-32)	3.7 (0.4-18)
Age at shunt procedure (years)	2.6 (0.2-12)	1.7 (0.1-7)	1.7 (0.1-11)
Age at first MRI (years)	31 (18-65)	28 (17-61)	25 (17-57)
RV-EDV-I (ml/m^2)	124±22	147±40	158±45
RV-ESV-I (ml/m^2)	68±33	87±37	89±35
RV-EF (%)	48±11	41±11	45±10
PR (%)	20±17	32±17	41±15

EDV-I = end-diastolic volume index, EF = ejection fraction, ESV-I = end-systolic volume index, PR = pulmonary regurgitant fraction, LV = left ventricle, RV = right ventricle

Baseline

Patient characteristics are shown in table 3.1. Baseline characteristics did not differ between patients with 1 and patients with 2 or more MR examinations. Of the 142 patients, 41 patients underwent the M / V procedure at initial repair, 23 patients received a RVP without crossing the pulmonary annulus, and 78 patients underwent a TAP procedure. The degree of PR was highest in the TAP group (41±15%), followed by the RV patch group (32±17%) and lowest in the group without a patch (20±17%, p<0.001). Furthermore, RV-EDV-I showed the same pattern (figure 3.2); RV-EDV-I was significantly higher in the TAP group (158±45ml) compared to the RVP and M / V groups (147±40ml and 124±22ml, p<0.001).

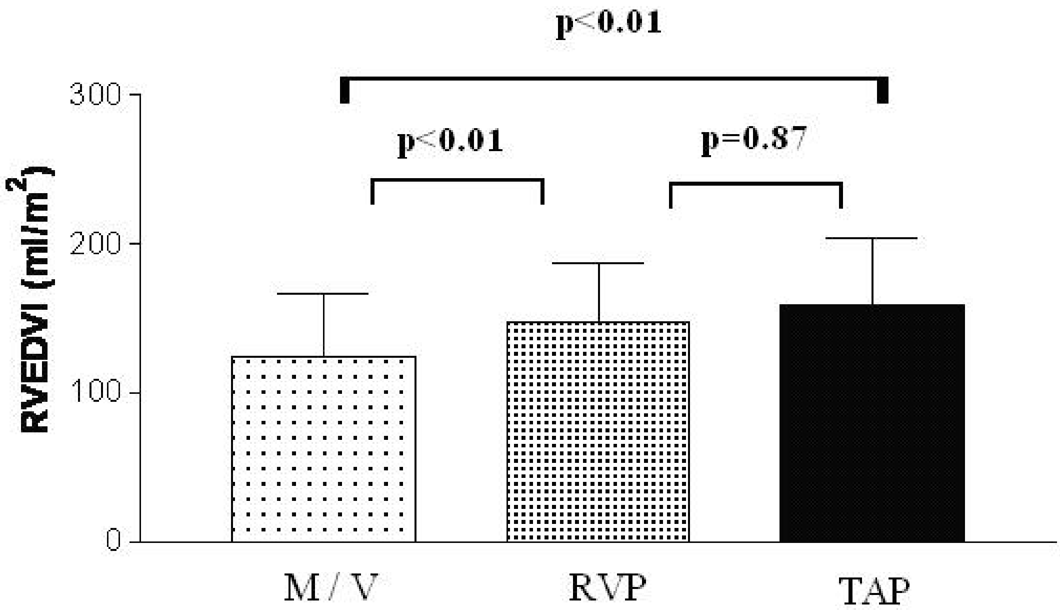

Figure 3.2. *Right ventricular end-diastolic volume, indexed for body surface are (RV-EDV-I) at baseline for different types of initial repair. RV-EDV-I was highest in patients who underwent a transannular patch procedure (TAP).*
M / V = myectomy / valvulotomy, RVP = right ventricular patch, TAP = transannular patch.

RV-EDV-I and RV-ESV-I, a measure of RV systolic function, were both independently predicted by the amount of PR (Beta 0.52 and 0.48 respectively, p<0.001). Therrien et al. recently reported that in patients with a RV-EDV-I of more than 170 ml2, no normalization of the RV volumes can be achieved after PVR [9]. In the M / V group, only 7/41 patients had a RV-EDV-I of more than 170 ml2, while in the RVP and the TAP group respectively 8/23 and 27/78 patients RV-EDV-I exceeded 170 ml2 ($p<0.001$ between M / V group and RVP / TAP groups).

Time course of RV function

In the TAP group, both RV-EDV-I and RV-ESV-I increased significantly (2.2 ± 0.68 ml/m^2 ($p<0.001$) and 1.1 ± 0.57 ml/m^2 per year ($p=0.001$), respectively), while RV-EF decreased by 0.37 ± 0.15% per year ($p=0.01$). In the other 2 groups RV dimensions and RV-EF remained unchanged. PR did not change significantly in any group. These results indicate differential patterns of RV function deterioration for different types of initial surgical repair (figure 3.3).

Predictors for outcome after initial repair

After correction for the age at repair and patient's sex, the type of initial repair was independently associated with the need for PVR. Patients with a TAP had the highest rate of PVR, compared to the M / V group (HR 2.2, $p=0.015$). However, no significant difference was observed between the RVP and the TAP group (HR 1.0, $p=0.99$).

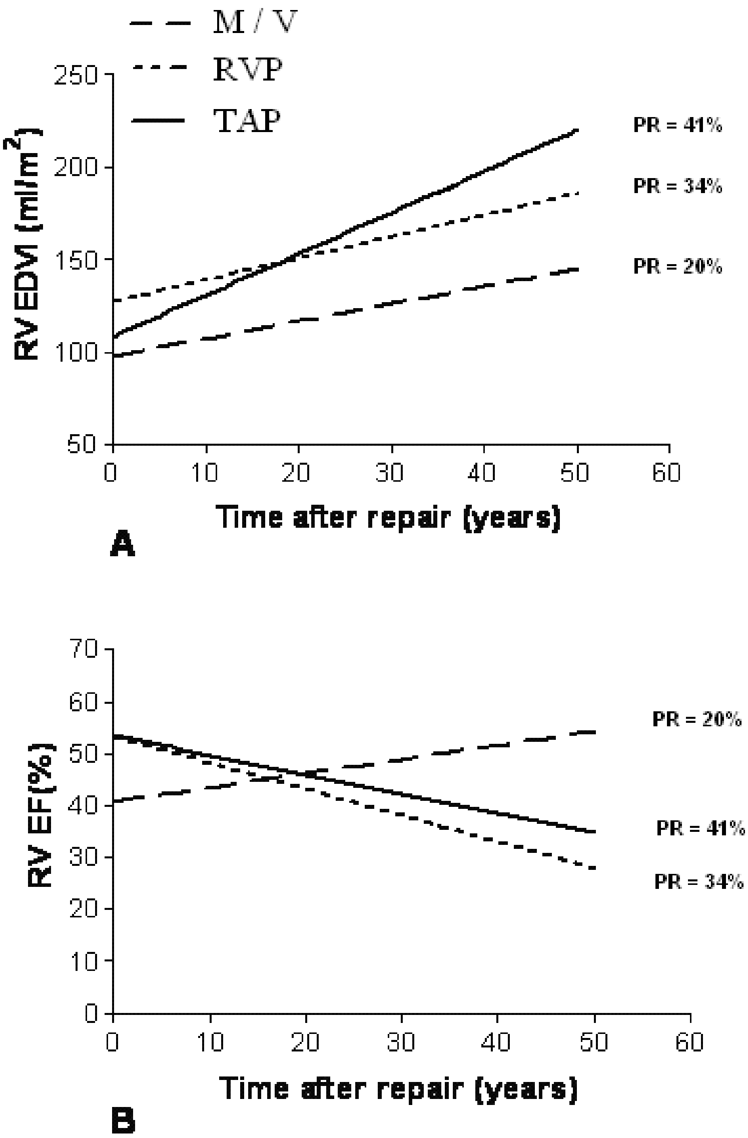

Figure 3.3. *Time course of the right ventricular end-diastolic volume and right ventricular ejection fraction for the different types of initial repair. Right ventricular end-diastolic volume (A) only increased significantly over time (P<0.05) in the group with patients after transannular patch repair. Right ventricular ejection fraction (B) deteriorated (P<0.05) in the groups with patients after both transannular patch and right ventricular patch repair.*

M / V = myectomy / valvulotomy, RVP = right ventricular patch, TAP = transannular patch, PR = pulmonary regurgitation, RV-EDV-I = right ventricular end-diastolic volume indexed for body surface area, RV-EF = right ventricular ejection fraction.

Discussion

To our best knowledge this is the first study showing the haemodynamic effects of the common types of initial TOF repair on RV function assessed by serial cardiac MRI. The use of a TAP in initial repair for TOF is associated with a higher degree of PR and consequently larger RV size. Deterioration over time of RV dilatation and function occurred only in patients with a TAP, whereas RV dimensions remained unchanged in patients without a patch or a patch confined to the right ventricle. These results indicate that the degree of PR and RV dilatation is dependent on the surgical technique for TOF correction. TAP is associated with more severe PR and deteriorating RV dilatation with a consequently higher rate of PVR.

In our group, the highest RV volumes and the highest degrees of PR at baseline were found in the TAP group. Patients who underwent a M / V procedure had the lowest degree of PR at baseline, whereas patients following a RVP procedure had a degree of PR higher than in the M / V group, but lower than in the TAP group. These findings are in accordance with the study of d'Udekem [2], who showed more PR in patients with a RVP or TAP compared to patients who underwent the M / V procedure without a patch. In their study, the use of a TAP was invariably associated with more severe PR as compared with patients with a patch confined to the right ventricle or no patch at all. Several other studies have demonstrated the deleterious effects of PR on RV volumes and function [14,15]. Serial MR examinations showed a gradual deterioration of RV volumes and function in patients who underwent a TAP procedure in infancy, whereas no significant changes were found in patients after RVP or M/V procedures. However, even in the RVP and the M / V group RV dimensions were significantly higher than in the general population [16]. Other haemodynamic parameters did not differ between the 3 groups at baseline. The degree of PR seems therefore the main determinant for the time course of RV volumes.

Since RV function deterioration mainly occurred in patients with PR fraction of 40% or more, we speculate that there may be a threshold for the degree of PR to cause progressive RV dilatation. If PR does not exceed the threshold, the increased ventricular load presumably leads to increased wall pressure and consequently increased cardiac output (ascending part of Frank-Starling curve). When the degree of PR exceeds the threshold, the increased ventricular load cannot longer be compensated by increased wall pressure (descending part of Frank-Starling curve) leading to further dilatation of the ventricle. However, further studies are needed to demonstrate the existence of such a threshold that leads to RV dilatation and to assess which factors influence the cutoff value of this threshold.

The clinical significance of progressive RV dilatation was recently underscored by the publication of Knauth et al. [17] They found that major adverse clinical events such as death, NYHA class III or IV and sustained ventricular tachycardia were predicted by severe RV dilatation and either LV or RV dysfunction assessed by cardiac MRI. They found no direct correlation between the degree of PR and adverse clinical events, however, the degree of PR was inversely correlated with RV function.

Previous studies have shown the beneficial effects of PVR in TOF patients with severe RV dilatation due to long standing PR. Both systolic and diastolic function improve following PVR, yet optimal timing remains controversial. Recent studies demonstrated improvement in systolic function in a group of TOF patients, however, normalization of RV dimensions was only observed in patients with an RV-EDV-I of less than 160 - 170 ml/m^2 before valve replacement [8,9]. On the other hand, replacing the pulmonary valve too early may increase the number of re-operations since pulmonary homografts may not last more than 10-15 years [18].

In our group PVR was more often performed in patients who had underwent RVP or TAP repair reflecting the higher degree of PR and concomitant RV dilatation in these patients as compared to patients without patch repair. A RV-EDV-I of more than 170 ml2 was more common in the RV patch and the transannular patch groups than in the M / V group, reflecting the need for earlier PVR in order to achieve normalization of RV volumes in these patients. d'Udekem et al. also found an increased need for PVR in patients with a TAP. In their study no statistically significant difference was found as well in the rate of PVR between patients with a TAP and patients with a RVP [19].

Our results indicate that timing of PVR should be based on the combination of the degree of PR and RV dilatation. Patients with mild to moderate PR and relatively preserved RV function and dimensions can safely be followed, whereas patients with moderate to severe PR should be carefully monitored even in the absence of severe RV dilatation as RV function and volumes are likely to deteriorate over time.

A limitation of this study is the fact that not all patients underwent more than one MR examination. Due to the retrospective design of the study, follow-up MR examinations were only performed when the clinician needed more information on the haemodynamic status of the patients. However, baseline characteristics for patients with one MRI compared with patients with more than one MRI did not differ significantly.

Conclusion

PR appears to be the most important parameter for predicting the time course of RV failure as moderate to severe PR leads to gradual deterioration of RV dimensions and function. Since TAP and RVP at initial repair is associated with a higher degree of PR than repair without the insertion of a patch, patients with a TAP should be carefully monitored for RV function deterioration. Therefore these results may guide risk stratification and therapeutic interventions in TOF patients late after initial repair.

References

1 Kolcz J, Pizarro C. Neonatal repair of tetralogy of Fallot results in improved pulmonary artery development without increased need for reintervention. Eur J Cardiothorac Surg 2005;28:394-9.

2 d'Udekem Y, Ovaert C, Grandjean F et al. Tetralogy of Fallot: transannular and right ventricular patching equally affect late functional status. Circulation 2000;102(19 Suppl 3):116-122.

3 Bove EL, Byrum CJ, Thomas FD et al. The influence of pulmonary insufficiency on ventricular function following repair of tetralogy of Fallot. Evaluation using radionuclide ventriculography. J Thorac Cardiovasc Surg 1983;85:691-6.

4 Cheung MM, Konstantinov IE, Redington AN. Late complications of repair of tetralogy of Fallot and indications for pulmonary valve replacement. Semin Thorac Cardiovasc Surg 2005;17:155-9.

5 Vliegen HW, van Straten A, de Roos A et al. Magnetic resonance imaging to assess the hemodynamic effects of pulmonary valve replacement in adults late after repair of tetralogy of fallot. Circulation 2002;106:1703-7.

6 Yemets IM, Williams WG, Webb GD et al. Pulmonary valve replacement late after repair of tetralogy of Fallot. Ann Thorac Surg 1997;64:526-30.

7 Bove EL, Kavey RE, Byrum CJ, Sondheimer HM, Blackman MS, Thomas FD. Improved right ventricular function following late pulmonary valve replacement for residual pulmonary insufficiency or stenosis. J Thorac Cardiovasc Surg 1985 July;90(1):50-5.

8 Oosterhof T, van Straten A, Vliegen HW et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. Circulation 2007;116:545-51.

9 Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. Am J Cardiol 2005;95:779-82.

10 Murphy JG, Gersh BJ, Mair DD et al. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. N Engl J Med 1993;329:593-9.

11 Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol 1997;30:1374-83.

12 van der Geest RJ, Reiber JH. Quantification in cardiac MRI. J Magn Reson Imaging 1999;10:602-8.

13 Pattynama PM, Lamb HJ, Van der Velde EA, van der Geest RJ, van der Wall EE, de RA. Reproducibility of MRI-derived measurements of right ventricular volumes and myocardial mass. Magn Reson Imaging 1995;13:53-63.

14 Davlouros PA, Kilner PJ, Hornung TS et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol 2002;40:2044-52.

15 Abd El Rahman MY, Abdul-Khaliq H, Vogel M, Alexi-Meskishvili V, Gutberlet M, Lange PE. Relation between right ventricular enlargement, QRS duration, and right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation after surgical repair. Heart 2000;84:416-20.

16 Tandri H, Daya SK, Nasir K et al. Normal reference values for the adult right ventricle by magnetic resonance imaging. Am J Cardiol 2006;15;98:1660-4.

17 Knauth AL, Gauvreau K, Powell AJ et al. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. Heart 2008;94:211-6.

18 Boethig D, Goerler H, Westhoff-Bleck M et al. Evaluation of 188 consecutive homografts implanted in pulmonary position after 20 years. Eur J Cardiothorac Surg 2007;32:133-42.

19 d'Udekem Y, Rubay J, Shango-Lody P et al. Late homograft valve insertion after transannular patch repair of tetralogy of Fallot. J Heart Valve Dis 1998;7:450-4.