Clinical condition at mid-to-late follow-up after transatrial–transpulmonary repair of tetralogy of Fallot

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Objectives: To assess the clinical condition at mid-to-late follow-up in tetralogy of Fallot corrected by a transatrial–transpulmonary approach at a young age and to identify risk factors associated with right ventricular dilation/dysfunction and with decreased exercise tolerance.

Methods: Patients with tetralogy of Fallot underwent cardiac magnetic resonance imaging, maximal bicycle ergometry, electrocardiography, Holter monitoring, and spirometry. Multivariate linear regression analyses were used to determine independent predictors for selected clinical parameters.

Results: Fifty-nine patients (mean ± SD), age at repair 0.9 ± 0.5 years, interval since repair 14 ± 5 years, were included. The median pulmonary regurgitant fraction was 32% (0%-57%). Compared with published data on healthy controls, Fallot patients had significantly larger right ventricular end-diastolic and end-systolic volumes and smaller right ventricular and left ventricular ejection fractions. Maximum oxygen consumption was 97% ± 17% and maximum workload 89% ± 13% of predicted. Median QRS duration was 110 ms (82–161 ms). No important ventricular arrhythmias were found. Compared with patients without a transannular patch, patients with a patch had more pulmonary regurgitation, a larger right ventricle, worse right ventricular and left ventricular ejection fractions, but comparable exercise capacity. Multivariate regression analysis identified the following independent determinants for larger right ventricular volumes: longer interval since repair, longer QRS duration, and higher pulmonary regurgitation percentage. The following were independent determinants for smaller right ventricular ejection fraction: abnormal right ventricular outflow tract wall motion, longer interval since repair, and longer QRS duration. For smaller maximum oxygen consumption, the independent determinants were smaller right ventricular ejection fraction and longer QRS duration.

Conclusions: At mid-to-late follow-up, clinical condition in tetralogy of Fallot corrected according to contemporary surgical approaches appears well preserved. However, even these patients show right ventricular dilation and dysfunction associated with impaired functional capacity. Abnormalities relate to right ventricular outflow tract motion abnormalities, longer interval since repair, longer QRS duration, and more severe pulmonary regurgitation.

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Over the past decades, perioperative mortality of correction for tetralogy of Fallot (TOF) decreased for all ages, including infants.[1,2] Repair at a young age shortens the period the patient is subjected to systemic hypoxemia and to right ventricular (RV) pressure overload. These considerations have led to a trend of primary correction performed at a young age, aimed at optimal relief of RV outflow tract (RVOT) obstruction and closure of the VSD.[1,2] In addition, the

Abbreviations and Acronyms

CMR = cardiac magnetic resonance imaging
FVC = forced vital capacity
LV = left ventricular
PR = pulmonary regurgitation
RQ = respiratory quotient
RV = right ventricular
TAP = transannular patch
TE = echo time
TOF = tetralogy of Fallot
Vo_{2max} = maximum oxygen consumption
VSD = ventricular septal defect

concept of transatrial–transpulmonary repair for TOF gained popularity.[3] This concept aims at reducing the side effects associated with a ventriculotomy, such as RV myocardial and coronary artery damage. Outcome of TOF repair has been described extensively. Pulmonary regurgitation (PR) is a crucial factor in long-term outcome.[4] There is a lack of studies reporting on long-term follow-up, acquired with appropriate tools, in patients with TOF repaired according to recent surgical strategies. Furthermore, most studies have included a mixture of patients with optimal and suboptimal surgical results, such as residual VSD or important pulmonary stenosis. This precludes assessment of optimal long-term effects of repair of TOF and of factors associated with decline in clinical state after optimal repair, that is, clinical condition in patients with (inevitable) PR, but without additional problems. Therefore, the present study aimed (1) to assess clinical condition at midterm to long-term follow-up, including assessment of biventricular volumes and function by cardiac magnetic resonance imaging (CMR) and (2) to identify factors associated with RV dilation, RV dysfunction, and decreased exercise tolerance in patients with TOF operated on at a young age by the transatrial–transpulmonary approach and without residual VSD or important pulmonary stenosis.

Patients and Methods

A cross-sectional study of patients after surgical repair of TOF was performed. The local medical ethics committee approved our study protocol. Informed consent was obtained from patients or parents if patients were not of the legal age to provide consent. Patients were included for data collection between September 2002 and November 2004. The following inclusion criteria were used: (1) complete repair of TOF without associated cardiac lesions, including double-outlet right ventricle (except patent ductus arteriosus), (2) age at repair 24 months years or younger, (3) transatrial–transpulmonary approach to repair, and (4) duration of postrepair follow-up of 5 years or more. Patients with one or more of the following criteria were excluded: residual VSD, residual pulmonary stenosis (echo Doppler mean gradient $>$ 30 mm Hg), repair with a homograft, mental retardation, and known extracardiac pathologic condition. Criteria were reviewed by use of the patient's medical records. Preoperative hemodynamic data were obtained from diagnostic heart catheterization reports.

Magnetic Resonance Imaging Protocol

A 1.5-Tesla Signa CVi scanner was used with software releases V8 and V9.1 (General Electric, Milwaukee, Wis). A cine volumetric dataset was acquired in short-axis direction using a 2-dimensional fast imaging employing steady-state acquisition sequence (steady-state free precession). Imaging parameters were as follows: flip angle = 45°, echo time (TE) set at minutes full, repetition time (TR) = 3.4–3.6 ms, 8-to 9-mm slice thickness, 0- to 1-mm interslice gap, 12 views/segment, readout bandwidth = 111 KHz, a square field of vision (30–34 cm), and a scanning matrix of 160 · 128. Twenty-four phases per cardiac cycle were reconstructed retrospectively.

Pulmonary valve flow measurements were performed perpendicular to flow using a standard 2-dimensional retrospectively gated flow-sensitized sequence. Thirty cardiac phases were reconstructed retrospectively. Imaging parameters were as follows: 2-dimensional fast spoiled gradient echo, TR = 6 to 7 ms, TE = 3 ms, flip angle = 20°, readout bandwidth = 90 KHz, 6-mm slice thickness, 6 views/segment, a rectangular field of vision (75% in phase encoding direction), and a scanning matrix of 256 · 128.

Magnetic Resonance Image Analysis

CMR studies were analyzed on an Advanced Windows workstation (General Electric, Milwaukee, Wis). Flow images were quantitatively analyzed with the Flow analysis software package V2.0 (Medis Medical Imaging Systems, Leiden, The Netherlands). Residual pulmonary stenosis was calculated with the simplified Bernoulli equation ($\Delta P = 4 \cdot Vmax^2$). Volumetric data were quantitatively analyzed with the Mass analysis software package V3.1 (Medis Medical Imaging Systems, Leiden, The Netherlands), with parameters assessed according to analysis techniques widely reported in the literature.[5] Volumetric CMR parameters were indexed for body surface area unless specified otherwise. Values outside the mean ± 2 SD range in healthy controls were defined to be abnormal. On the cines an experienced observer assessed wall motion in the RVOT. Abnormal wall motion was defined as absent or outward movement of part of the RVOT wall during systole. To calculate the PR fraction, amount of PR was normalized for the systolic stroke volume across the pulmonary valve (PR percentage e = Backward flow/Systolic forward flow · 100%). Critical upper limits for RV end-diastolic volume, 200 mL/m^2 in children and 170 mL/m^2 in adults, associated with absent return of RV volume to normal size after pulmonary valve replacement have been reported and were applied on our population.[6,7]

Bicycle Ergometry

Patients performed a symptom-limited bicycle exercise test on a Jaëger Oxycom Champion System (Viasys Healthcare, Hoechberg, Germany), allowing breath-by-breath-ergometry. Workload was increased with 10 to 20 Watts per minute. Patients were encouraged to perform to exhaustion. Tests were regarded as maximal with a respiratory quotient (RQ) of 1.05 or greater in children and 1.10 or greater in adults at peak exercise. Exercise capacity was compared with that of normal individuals, corrected

for age, sex, and weight.[8] Values greater than 85% of predicted were considered normal.

Spirometry

Preceding the exercise test, patients performed a standard maximal forced vital capacity (FVC) maneuver using a dry rolling seal spirometer (Jaëger, Würzburg, Germany). From the obtained loops the following parameters were derived: FVC, forced expiratory volume in the first second (FEV_1), ratio FEV_1/FVC, and maximum expiratory flow at 25% of FVC. Results were compared with those from normal individuals corrected for age, gender, and body composition and expressed as percentages of predicted values.

Electrocardiogram

A standardized 12-lead electrocardiogram was obtained to assess QRS (ms), QT corrected for heart rate (QTc; ms), and JT corrected for heart rate (JTc; ms) duration. A 24-hour Holter monitoring was performed on a day with usual activities.

Statistical Analysis

CMR results of patients were compared with a reference population from the literature using the 2-sample *t* test.[9] Data were $\log_{10}$-transformed when appropriate to obtain approximately normal distribution. Results are expressed as mean ± SD for normally distributed data, otherwise as the median and range. Bivariate correlation coefficients were calculated by the Spearman method. Multivariate linear regression analyses (backward stepwise regression method) were used to determine major independent predictors for outcome variables. Only variables significant in univariate analysis were included in these multivariate analyses. Percentages were compared by the χ^2 test. Analysis was performed with the SPSS-PC statistical software package version 11.5 (SPSS, Chicago, Ill).

Results

Patient Characteristics

Records of 169 eligible patients alive in 2002 and operated on between 1980 and 1997 before the age of 2 years by a transatrial–transpulmonary approach at the Erasmus MC Rotterdam or the University MC Utrecht were checked. Reasons for exclusion were as follows: residual VSD (n = 3), residual RVOT stenosis (>30 mm Hg) (n = 11), repair with a homograft (n = 15), mental retardation (n = 16), extracardiac disease (n = 7), and lost to follow-up (n = 32). Eighty-five patients fulfilled all inclusion criteria and received an invitation for this study. Sixty-three (74%) patients agreed to participate. Four of our youngest participants (aged 5.9–6.5 years) did not complete the entire protocol and were excluded from all results. The characteristics of the remaining 59 patients are shown in Table 1. Patients who refused to participate and those lost to follow-up did not differ from participants in mean age at repair, interval since repair, incidence of staged repairs, or gender distribution. Patients did not use cardiac medication, 51 (86%) were in New York Heart Association class I (86%), and 8 (14%) in class II.

TABLE 1. Patient characteristics

	Patient total, n = 59 (100%)
Gender (M/F)	41/18
Age at repair (y)	0.8 (0.2–2.0)
Age at study (y)	15 (6–23)
Interval since repair (y)	14 (6–23)
BSA (m^2)	1.5 ± 0.4
Previous Blalock-Taussing shunt	3 (5%)
Preoperative measures	
RV/aortic peak pressure ratio	1.0 ± 0.1
RV peak pressure (mm Hg)	88 ± 9
Oxygen saturation (%)	87 (62–100)
Residual pulmonary stenosis (mm Hg)	9 (3–29)

Data given are mean ± SD and median (range). *BSA,* Body surface area; *RV,* right ventricle.

In 42 (71%) patients a transannular patch (TAP) repair was performed. In the remaining 17 (29%) patients desobstruction of the RVOT was achieved by a combination of the following techniques: infundibulectomy, valvulotomy, commissurotomy, and partial valvectomy. Before repair, patients with a TAP had a lower arterial oxygen saturation (86% ± 9% vs 92% ± 9%; $P < .05$) and a higher RV/aortic peak pressure ratio (1.0 ± 0.1 vs 0.9 ± 0.1; $P < .05$) than did patients without a TAP. TAP repairs were performed at a younger age (median age at repair 0.6 years [0.2–2.0 years] versus 1.1 [range 0.3–2.0]; $P < .05$). Interval since repair was comparable between patients with a TAP and those without (15 ± 5 years versus 13 ± 4 years; $P = .14$).

CMR

The median value for PR percentage was 35% (range 0%–57%). Patient CMR data were compared with data from the literature assessed in healthy controls (Table 2).[9] Differences in CMR findings between patients with and without a TAP are shown in Table 3. Abnormal wall motion in the RVOT region was diagnosed in 41 (69%) patients. Cumulative incidence of abnormal wall motion was larger in patients with a TAP than in those without (37/42 patients vs 4/17; χ^2 test < .001). Similar differences as for patients with or without a TAP were found with regard to PR, biventricular size, and ejection fraction when comparisons were made for patients with abnormal RVOT wall motion versus those with normal wall motion (data not shown).

The RV end-diastolic volume was greater than 170 mL/m^2 in 14 (24%) patients and more than 200 in 4 (7%). Compared with patients with an RV end-diastolic volume of 170 mL/m^2 or less, patients with an RV end-diastolic volume greater than 170 had a smaller RV ejection fraction (50% ± 6% vs 44% ± 5%; $P < .05$), comparable left ventricular (LV) ejection fraction (57% ± 6% vs 55% ± 6%; not significant), and worse exercise capacity (percent-

TABLE 2. Biventricular CMR results in patients and controls

	TOF patients		Controls		Abnormal†
No. of patients	59		16		
Age (y)	15 ± 5		18 ± 2		
	Mean ± SD	**Range**	**Mean ± SD**	**Limit**	**N (%)**
RVEDV (mL/m^2)	139 ± 37*	85–237	79 ± 9	97 (UL)	50 (85%)
RVESV (mL/m^2)	72 ± 26*	35–145	32 ± 7	56 (UL)	50 (85%)
RVSV (mL/m^2)	66 ± 14*	36–100	49 ± 6	61 (UL)	38 (64%)
RVEF (%)	49 ± 6*	32–60	61 ± 6	49 (LL)	29 (49%)
LVEDV (mL/m^2)	81 ± 12	61–109	79 ± 9	97 (UL)	7 (12%)
LVESV (mL/m^2)	36 ± 8*	16–53	29 ± 7	43 (UL)	10 (17%)
LVSV (mL/m^2)	46 ± 7	31–67	49 ± 6	37 (LL)	4 (7%)
LVEF (%)	56 ± 6*	42–74	63 ± 6	51 (LL)	7 (12%)

Limits of normal: *UL* (upper limit) = mean + 2 SD; *LL* (lower limit) = mean − 2 SD. *CMR,* Cardiac magnetic resonance imaging; *TOF,* tetralogy of Fallot; *RVEDV,* right ventricular end-diastolic volume; *RVESV,* right ventricular end-systolic volume; *RVSV,* right ventricular stroke volume; *RVEF,* right ventricular ejection fraction; *LVEDV,* left ventricular end-diastolic volume; *LVESV,* left ventricular end-systolic volume; *LVSV,* left ventricular stroke volume; *LVEF,* left ventricular ejection fraction; *SD,* standard deviation. *Significant difference ($P < .05$) compared with controls. †Number of patients with abnormal CMR results (above UL or below LL of relevance).

age of predicted maximum (peak) oxygen consumption [Vo_{2max}] 99% ± 18% vs 90% ± 11%; $P < .05$). All patients with RV end-diastolic volume greater than170 mL/m^2 had 12 years or more of follow-up (median 18 years, range 12–23) and a PR percentage greater than 30% (median 46%, range 31%–54%).

TABLE 3. Comparison of patients according to presence of a TAP in the RVOT*

	No patch, n = 17 (29%)	TAP repair, n = 42 (71%)
PR percentage	14 ± 12	40 ± 11†
Residual pulmonary stenosis	13 ± 7	9 ± 6†
RVEDV (mL/m^2)	106 ± 19	152 ± 35†
RVESV (mL/m^2)	51 ± 12	81 ± 25†
RVSV (mL/m^2)	55 ± 10	71 ± 13†
RVEF (%)	52 ± 6	47 ± 6†
RVFWM (g/m^2)	20 ± 4	26 ± 6†
LVEDV (mL/m^2)	82 ± 12	81 ± 12
LVESV (mL/m^2)	34 ± 8	37 ± 8
LVSV (mL/m^2)	48 ± 8	45 ± 7
LVEF (%)	59 ± 6	55 ± 5†
LVM (g/m^2)	52 ± 9	53 ± 10

Data given are mean ± SD. *TAP,* Transannular patch; *RVOT,* right ventricular outflow tract; *PR,* pulmonary regurgitation; *RVEDV,* right ventricular end-diastolic volume; *RVESV,* right ventricular end-systolic volume; *RVSV,* right ventricular stroke volume; *RVEF,* right ventricular ejection fraction; RVFWM, right ventricular free wall mass; *LVEDV,* left ventricular end-diastolic volume; *LVESV,* left ventricular end-systolic volume; *LVSV,* left ventricular stroke volume; *LVEF,* left ventricular ejection fraction; *LVM,* left ventricular mass. All CMR parameters were indexed for body surface area. *Similar differences with regard to PR, biventricular size, wall mass and EF were found when comparisons were made for patients with normal and abnormal RVOT wall-motion (data not shown). †Significant difference compared with patients without a patch in the RVOT (*t* test, $P < .05$)

Electrocardiogram and Holter Monitoring

All patients were in sinus rhythm. Right bundle branch block was diagnosed in 80% of patients. Median QRS duration was 110 ms (range 82–161 ms), mean QTc duration was 408 ± 32 ms, and mean JTc duration was 270 ± 23 ms. No differences were found for QRS duration ($P = .47$), QTc duration ($P = .39$), and JTc duration ($P = 0.26$) between patients with or without a TAP.

During 24-hour Holter monitoring, 5 patients showed one or more cardiac pauses of more than 1.9 second. The longest observed pause lasted 2.3 seconds. Two patients, both with a TAP, showed a nonsustained ventricular tachycardia run of respectively 3 and 4 complexes at heart rates of 174 and 108 beats/min with a QRS duration in sinus rhythm of 105 and 130 ms, respectively.

Spirometry

Mean FEV_1 was 99% ± 12% of predicted. Mean FVC was 94% ± 12% of predicted. The median FEV_1/FVC ratio was 89% (range 75%–100%). Mean maximum expiratory flow at 25% of FVC was 89% ± 31% of predicted. Mean FVC of predicted tended to be higher in patients without a TAP (97% ± 14% vs 90% ± 12%; $P = .05$). The other parameters were not different between patients with and without a TAP.

One patient showed severe obstructive abnormalities, and exercise results of this patient were excluded from analysis. The parameters derived from the maximal flow-volume loops showed no significant correlations with percentage of predicted Vo_{2max}.

Bicycle Ergometry

The patient with obstructive airway disease was excluded, 1 patient declined the test, and 1 patient could not complete

TABLE 4. Predictors of peak oxygen consumption (Vo_2)

	Univariate analysis		Multivariate analysis	
Predictor	**Regression coefficient ± SE**	***P* value**	**Regression coefficient ± SE**	***P* value**
Dependent: Vo_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)				
LVSV (mL/m^2)	0.5 ± 0.2	.002	0.4 ± 0.1	.001
Gender (M/F)	−7.0 ± 2.2	.002	5.9 ± 1.8	.002
Interval since repair (y)	−0.6 ± 0.2	.004	−0.5 ± 0.2	.004
QRS duration (ms)	−0.15 ± 0.06	.008	−0.10 ± 0.05	.04
Constant			34.9 ± 7.5	—
RVEF (%)	0.53 ± 0.16	.002		NS
PR percentage	−0.17 ± 0.06	.009		NS
TAP (yes/no)	4.8 ± 2.2	.04		NS
RVOT motion (abnormal/normal)	−5.3 ± 2.2	.02		NS
RV peak pressure (mm Hg)	−0.18 ± 0.08	.03		NS
Dependent: Vo_2 percentage of predicted				
RVEF (%)	1.6 ± 0.3	<.001	1.3 ± 0.3	<.001
QRS duration (ms)	−0.4 ± 0.1	.001	−0.2 ± 0.1	.05
Constant			59.4 ± 24.1	—
RVESV (mL/m^2)	−0.23 ± 0.09	.009		NS
LVSV (mL/m^2)	0.8 ± 0.3	.02		NS
LVEF (%)	1.2 ± 0.4	.002		NS
Interval since repair (y)	−1.5 ± 0.4	.001		NS
RV peak pressure (mm Hg)	−0.39 ± 0.16	.02		NS

Data given are regression coefficients ± standard errors. R^2 for the multiple regression model of Vo_2 ($mL \cdot kg^{-1} \cdot min^{-1}$) and Vo_2 (percentage of predicted) were respectively 0.49 and 0.36.

LVSV, Left ventricular stroke volume; *RVEF,* right ventricular ejection fraction; *PR,* pulmonary regurgitation; *TAP,* transannular patch; *RVOT,* right ventricular outflow tract; *RV,* right ventricular; *RVESV,* right ventricular end-systolic volume; *LVSV,* left ventricular stroke volume; *LVEF,* left ventricular ejection fraction; *NS,* not significant.

the test as a result of technical problems. Exercise data reflect results of the remaining 56 patients. Mean RQ at peak exercise was 1.2 ± 0.1. All patients reached our RQ criteria at peak exercise. Age at study correlated positively with RQ at peak exercise ($r = 0.44$; $P < .001$) and RQ during initial recovery ($r = 0.69$; $P < .001$). Vo_{2max} was 40 ± 8 $mL \cdot kg^{-1} \cdot min^{-1}$, or 97% ± 17% of predicted Vo_{2max} ($P = .20$), with a value less than 85% found in 14 (25%) patients. Mean peak workload was 149 ± 62 Watts, or 89% ± 13% of predicted ($P < .05$), with value less than 85% found in 18 (32%) patients.

Percentage of predicted workload and percentage of predicted Vo_{2max} were not different between patients with a TAP and those without a TAP (respectively, 88% ± 11% vs 92% ± 17%; $P = .37$; and 96% ± 15% vs 99% ± 22%; $P = .59$). Percentage of predicted workload and percentage of predicted Vo_{2max} were smaller in patients with abnormal RVOT wall motion than in patients with normal motion (respectively, 86% ± 12% vs 95% ± 13%; $P < .05$; and 94% ± 16% vs 103% ± 19%; $P = .07$).

Determinants of Exercise Capacity

Factors significantly related to Vo_{2max} and percentage of predicted Vo_{2max} by univariate analysis were determined. Predictor variables originated from the following 3 sets of parameters: (1) parameters determined at prerepair diagnostic heart catheterization (RV peak pressure, arterial oxygen saturation, RV/aortic pressure ratio), (2) perioperative parameters (age at repair, TAP [0 = present, 1 = absent]), and (3) postoperative parameters (PR percentage, interval since repair, RVOT wall motion [0 = abnormal, 1 = normal], QRS duration, QTc, JTc, and all biventricular CMR determined measures).

Variables with significant relations (at the .05 level) identified by univariate analysis were used in multiple regression analysis to identify independent determinants. Results for both the univariate and multivariate linear regression analyses are shown in Table 4.

Determinants of RV CMR Measures and PR Percentage

RV CMR parameters and PR percentage were analyzed by the same procedures described in the previous paragraph. During analyses on RV end-diastolic volume, end-systolic volume, and ejection fraction, the corresponding LV parameter was introduced in the model. Mathematically related RV CMR measures were not used in one model. Results for both the univariate and multivariate linear regression analyses are shown in Table 5.

TABLE 5. Predictors of RV CMR measures

	Univariate analysis		Multivariate analysis	
Predictor	**Regression coefficient ± SE**	***P* value**	**Regression coefficient ± SE**	***P* value**
Dependent: RVEDV (mL/m^2)				
Interval since repair (y)	3.7 ± 0.9	<.001	1.4 ± 0.6	<.05
PR percentage (%)	1.5 ± 0.2	<.001	1.3 ± 0.2	<.001
LVEDV (mL/m^2)	1.3 ± 0.4	.001	1.5 ± 0.2	<.001
Constant			−54.8 ± 18.4	—
TAP (yes/no)	42 ± 9	<.001		NS
RVOT motion (abnormal/normal)	7 ± 9	<.001		NS
RV peak pressure (mm Hg)	1.0 ± 0.3	.005		NS
Dependent: Log_{10} RVESV (mL/m^2)				
Interval (y)	0.016 ± 0.003	<.001	0.007 ± 0.003	<.01
PR percentage	0.006 ± 0.001	<.001	0.005 ± 0.001	<.001
LVESV (mL/m^2)	0.009 ± 0.002	<.001	0.007 ± 0.002	<.001
QRS duration (ms)	0.003 ± 0.001	.02	0.001 ± 0.001	<.05
Constant			1.15 ± 0.09	—
RV peak pressure (mm Hg)	0.004 ± 0.001	.003		NS
TAP (yes/no)	0.17 ± 0.04	<.001		NS
Dependent: RVEF (%)				
Interval (y)	−0.59 ± 0.14	<.001	−0.3 ± 0.1	<.05
QRS duration (ms)	−0.12 ± 0.04	.007	−0.07 ± 0.03	<.05
LVEF (%)	0.49 ± 0.13	.03	0.5 ± 0.1	<.001
RVOT motion (abnormal/normal)	5.9 ± 1.6	<.001	−3.1 ± 1.4	<.05
Constant			39.1 ± 7.0	—
RV peak pressure (mm Hg)	−0.13 ± 0.06	.03		NS
PR percentage	−0.12 ± 0.05	.03		NS
TAP (yes/no)	−4.7 ± 1.7	.007		NS
Dependent: PR percentage				
TAP (yes/no)	22.5 ± 3.4	<.001	22.2 ± 3.3	<.001
RV peak presssure (mm Hg)	0.39 ± 0.14	.008	0.3 ± 0.1	.02
Constant			−5.7 ± 9.0	—
RVOT motion (abnormal/normal)	−17.9 ± 4.0	<.001		NS
Arterial oxygen saturation	−0.57 ± 0.21	.01		NS
Interval since repair (y)	0.83 ± 0.41	.05		NS
RV free wall mass (g/m^2)	1.1 ± 0.3	.001		NS

Data given are regression coefficients ± standard errors. R^2 for the multiple regression models of RVEDV, RVESV, RVEF and PR percentage were respectively 0.76, 0.72, 0.53 and 0.53. *RV,* Right ventricular; *CMR,* cardiac magnetic resonance imaging; *RVEDV,* right ventricular end-diastolic volume; *PR,* pulmonary regurgitation; *LVEDV,* left ventricular end-diastolic volume; *TAP,* transannular patch; *RVEF,* right ventricular ejection fraction; *LVEF,* left ventricular ejection fraction; *RVOT,* right ventricular outflow tract; *LVESV,* left ventricular end-systolic volume; *LVEF,* left ventricular ejection fraction.

Discussion

This study provides quantitative data on clinical status at mid-to-late follow-up in patients with TOF corrected at a relatively young age by a transatrial–transpulmonary approach and without other residual lesions but PR. TOF repair almost inevitably results in some degree of PR. Here the median PR percentage was 35% (range 0%–57%). As expected with considerable volume overload, RV volumes were markedly elevated in our patients, with mean values being approximately twice that in controls and values above the upper limit of normal found in 85% of our patients (Table 2). Furthermore, RV and LV ejection fractions were decreased compared with controls in, respectively, 49% and 12% of our patients. Despite these striking abnormalities, chronic RV volume overload seems to be well tolerated by these patients. All were in New York Heart Association class I (86%) or II (14%), all were in sinus rhythm, and none used cardiac medication. Mean percentage of predicted Vo_{2max} was not different from controls. Patients had normal lung function, and no important ventricular arrhythmias were encountered.

This study identified independent predictors of several undesirable, but common problems during the follow-up of TOF. The most important predictor of poorer exercise capacity was a lower RV ejection fraction, which in turn was best predicted by abnormal RVOT wall motion. Larger RV dilation and poorer RV ejection fraction were associated with a longer interval since repair. This suggests that, even

in patients with TOF corrected according to current surgical strategies and with optimal surgical result, gradual but slow deterioration of RV function with volume overload seems inevitable. Patients with already marked RV dilation subjected to chronic PR may have symptoms develop over time, which stresses the need for serial follow-up.

RVOT Function in Repaired TOF

Previous studies have demonstrated the negative impact of TAP repair on PR and RV size.[10] In our study, multivariate regression analysis showed that TAP repair was the most important independent predictor of PR percentage, with a 22% ± 3% point higher PR percentage in patients with a TAP than in those without a TAP (Table 5). A higher PR percentage independently predicted larger RV volumes, but not poorer RV ejection fraction. Poorer RV ejection fraction was independently predicted by abnormal RVOT wall motion. A previous study among adult Fallot patients, operated on at older ages than our patients, also found abnormal motion in the RVOT region to predispose for RV dysfunction.[10] Both that study and ours showed that abnormal wall motion is not restricted to patients with a TAP. This suggests wall motion abnormalities can be induced by other factors. Remarkably, Davlouros and associates[10] found no difference in incidence of wall motion abnormalities between patients with and without TAP, whereas this difference was clearly present in our patients. This may be explained by the different primary surgical approach used, with a primary ventriculotomy used in most of the cases reported by Davlouros' group.[10] However, other factors such as prolonged hypoxemia, present in the cases reported by Davlouros and colleagues,[10] cannot be ruled out to play a role in RV wall motion abnormalities. The influence of surgery in the RVOT region on long-term outcome has also been studied by comparing patients undergoing transventricular TOF repair with patients with isolated pulmonary valve stenosis treated by pulmonary commissurotomy.[11] Freedom of adverse events related to RV dilation (defined as cardiac death, reoperation, and New York Heart Association class ≥ II) was better in patients after isolated commissurotomy despite similar degrees of moderate and severe PR found in both patient groups. These findings suggest that limited RVOT surgery contributes to better long-term outcome, which is supported by our study. Whether or not the recently described reconstructive technique of the pulmonary valve by Sung and colleagues[12] further contributes to improved outcome remains a matter of ongoing observation.

QRS Duration

In TOF a QRS duration greater than 180 ms in adults and greater than 170 ms in children is known to predispose to malignant ventricular arrhythmia and sudden death.[13,14] QRS duration did not exceed 170 ms in our patients. Residual PR and subsequent RV dilation have been associated with QRS prolongation.[14-16] Pulmonary valve replacement has been shown to reduce QRS duration proportionally to the degree of RV volume reduction.[17,18] In our population, QRS duration was an independent predictor of RV volume but also of RV ejection fraction and exercise tolerance (Table 5). These predictive effects were present in the range below the reported critical values that predispose for arrhythmia and sudden death.

Prolongation of QRS duration has been related to electrical inhomogeneity.[19] In this regard, ventricular dyssynchrony has been observed in TOF. Cardiac resynchronization therapy in heart failure with prolonged QRS duration has been proven beneficial for ventricular contractile function, symptomatic status, and mortality.[20,21] Thus far, results in congenital heart disease including TOF have been promising.[19] The relations found for QRS duration with RV ejection fraction and exercise capacity in the present study suggest that functional gain may be achieved by cardiac resynchronization therapy in selected patients with TOF.

Long-term Outcome of TOF

Pulmonary valve replacement currently is the only widely accepted treatment for residual PR in TOF. Optimal timing of this procedure seems crucial, but criteria so far have not been established.[4] Newer imaging techniques, such as CMR, are expected to supply the data required to design such criteria. Several groups studied outcome of pulmonary valve replacement using serial CMR data.[6,7,22] An RV end-diastolic volume of 170 mL/m^2 or less in adults and 200 mL/m^2 or less in children was found to relate to adequate recovery of RV volume.[6,7] Our patients with an RV end-diastolic volume greater than 170 mL/m^2 had worse exercise capacity. Remarkably, all these patients had an interval since repair of 12 years or more and a PR percentage greater than 30%. Patients with a PR percentage of 30% or less did not demonstrate an RV end-diastolic volume of more than 170 mL/m^2, irrespective of follow-up duration. Most large CMR-based studies report on patients with TOF operated on according to different surgical strategies than our patients (older age at repair, staged repairs, primary RV ventriculotomy, repair with RV–pulmonary artery conduits).[10,23] We demonstrate that previously obtained CMR criteria also identify worse clinical status in patients operated on according to a currently widely accepted surgical approach. However, the long-term prognostic value of these criteria regarding mortality and morbidity still has to be determined in patients from any surgical era.[7]

Study Limitations

Because of the potential negative effect of a ventriculotomy on long-term clinical state, a transatrial–transpulmonary

approach was chosen in all patients. The frequent use of a TAP illustrates that total avoidance of a ventriculotomy in TOF is not feasible in clinical practice. Furthermore, it created the opportunity to evaluate the effect of a TAP on clinical condition. Inclusion criteria limit this study to patients with "isolated" PR. As such, our patients represent that part of daily clinical practice with optimally repaired initial pathology (VSD and RVOT obstruction). Because of the design, difficulties in data interpretation introduced with various forms of ventricular overload are avoided.

We used CMR reference values from healthy controls of the same age range, obtained and analyzed in similar ways as in the current study.[9] During the assessment of functional capacity, we did not account for level of physical training. The RQ at peak exercise indicates all patients performed maximally. As expected, results show higher RQ values in older patients. Therefore, peak results may better reflect maximal exercise capacity in older patients. This may have resulted in a slight underestimation of the magnitude of regression in exercise capacity over time.

The debate on optimal age at repair is still ongoing. As all our patients had corrective surgery after the age of 2 months, we can only speculate on further improvement of clinical state if surgical correction was done in the neonatal period. We did not find important effects of age at repair on the outcome measures shown in Tables 4 and 5.

Conclusions

The current study demonstrates that at mid-to-late follow-up, symptomatic status, exercise performance, and rhythm status remain relatively normal in patients with TOF after repair according to a transatrial–transpulmonary approach. Deterioration of RV function and exercise capacity correlate with a longer interval since repair, but these moderate associations cannot be used to predict the pace of decline in the individual patient. Our results suggest that further improvement of clinical condition may be obtained by improving preservation of RVOT function and by reducing the effect of electrical inhomogeneity. The evolution of CMR, electrocardiographic, and exercise data in this series, as well as the need for and the effects of interventions, should be re-evaluated in future studies.

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