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Factors associated with the need for pulmonary valve replacement in asymptomatic patients with isolated pulmonary regurgitation after repair of tetralogy of Fallot: a cardiac magnetic resonance study

Short title: Pulmonary valve replacement after repair of tetralogy of Fallot

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**Background:** Pulmonary regurgitation (PR) is the most common late complication in patients after repair of tetralogy of Fallot (TOF). The majority of patients remain asymptomatic over years but eventually the compensatory mechanisms fail leading to right ventricular (RV) dilatation and dysfunction, limited exercise capacity, ventricular arrhythmia, and sudden death.

**Aims:** To evaluate an association between cardiac magnetic resonance (CMR) parameters and the need for either surgical or percutaneous pulmonary valve replacement (PVR) in asymptomatic patients with significant PR after TOF repair.

**Methods:** Of 209 patients with repaired TOF who had undergone CMR study, we selected a group of 61 asymptomatic patients with moderate-to-severe PR and monitored them for up to 4 years (mean: 21.4 ± 13.7 months). We excluded patients with residual ventricular septal defect, peak RV outflow tract gradient ≥30 mmHg, or at least moderate tricuspid regurgitation.

**Results:** Receiver operating characteristics curve analyses revealed that RV volume to left ventricular volume (RV/LV) ratio (threshold >2.4) and PR fraction (PRF, threshold >33%) had acceptable discriminatory capacity to differentiate patients with the need for PVR from those treated conservatively. The Cox proportional-hazards regression and the Kaplan-Meier curves revealed that RV/LV ratio and PRF showed a significant association with the outcome. The combination of RV/LV ratio and PRF provided significant discrimination ($P = 0.0006$; log-rank test for trend).

**Conclusions:** The RV/LV ratio and PRF had a significant association with the need for PVR in asymptomatic patients with isolated moderate-to-severe PR after TOF repair.

**Key words:** cardiac magnetic resonance; outcome; pulmonary regurgitation; pulmonary valve replacement; tetralogy of Fallot
INTRODUCTION

Pulmonary regurgitation (PR) is the most common late complication in patients after repair of tetralogy of Fallot (TOF). The majority of patients remain asymptomatic over years but eventually the compensatory mechanisms fail leading to right ventricular (RV) dilatation and dysfunction, limited exercise capacity, ventricular arrhythmia, and sudden death [1,2]. The timing of pulmonary valve replacement (PVR), either percutaneous or surgical, in patients with repaired TOF remains controversial [1,2]. While the need for PVR in symptomatic patients is not questionable, performing PVR in asymptomatic subjects raises concerns about the risk-benefit ratio. Since an ideal valve substitute is yet to be found, an early surgery exposes a patient to the need for re-intervention in about 5-10 years after the index procedure with a considerable number of patients suffering from early homograft failure [3-5]. On the other hand, there are concerns that waiting too long leads to the point when RV dysfunction is irreversible and thus benefits of late PVR become fairly limited [6-9].

CMR is considered the reference standard for the quantification of PR and the assessment of RV size and function [1,2,10]. It would be of a particular clinical value to identify factors associated with the need for future PVR in asymptomatic patients with significant PR after TOF repair. Accordingly, we aimed to evaluate an association between CMR parameters and the need for future PVR in this population.

METHODS

Study subjects

Data from a high-volume tertiary adult congenital heart disease centre were retrospectively analysed. All patients after TOF repair who had undergone CMR study were identified. Patients with pulmonary atresia and ventricular septal defect were not included so that a homogeneous patient population could be achieved. Thereafter, individuals with moderate-to-
severe PR as assessed by echocardiography were selected. We excluded symptomatic patients, individuals with peak instantaneous RV outflow tract (RVOT) gradient ≥30 mm Hg, or residual ventricular septal defect. Additionally, patients with at least moderate tricuspid, aortic, or mitral regurgitation were excluded.

Patients were followed up for up to 49 months. Each patient gave a written informed consent for CMR study. The local Ethics Committee approved the analysis of medical records and computer databases. The study complies with the Declaration of Helsinki.

**CMR**

All CMR studies were performed with the use of a 1.5 T scanner (Avanto, Siemens, Erlangen, Germany). The size and the function of the ventricles (RV and left ventricular [LV] end-diastolic volumes [RVEDV and LVEDV, respectively], RV and LV end-systolic volumes [RVESV and LVESV], RV and LV ejection fractions [RVEF and LVEF, respectively], RV and LV masses [RVM and LVM, respectively]) were calculated by the dedicated software (Mass 6.2.1, Medis, Leiden, the Netherlands) on the basis of a stack of balanced steady-state free precession cine images acquired from the base to the apex. All volume and mass parameters were indexed to body surface area and expressed either in mL/m² or g/m². By dividing RVEDV by LVEDV, RV volume to LV volume (RV/LV) ratio was calculated [11]. Corrected RVEF was calculated by dividing the net pulmonary flow by RVEDV [12].

Pulmonary flow was derived from a phase sensitive gradient echo sequence with imaging plane located in the mid-point of the main pulmonary artery or conduit perpendicularly to the vessel wall. PR fraction (PRF = regurgitant volume/forward volume × 100%) and PR volume (PRV = regurgitant volume/body surface area) were calculated.

**Echocardiography**

All echocardiographic studies were performed with systems available commercially by physicians with experience in congenital heart diseases. The assessment of PR severity was
made by using different methods to corroborate each other [13]. The maximum velocity across RVOT was determined with continuous-wave Doppler imaging and peak instantaneous RVOT gradient was calculated with the use of the Bernoulli equation.

**Indications for PVR**

The decision about performing PVR was made by the consensus of a treating physician/physicians, a cardiosurgeon, and an interventional cardiologist, based on the comprehensive patients’ evaluation including clinical assessment, echocardiography, CMR, and in selected cases: cardiopulmonary exercise testing and Holter monitoring. The following situations were considered as an indication for PVR: (1) development of symptoms, (2) reduced exercise capacity, (3) progressive or severe RV dilatation, (4) moderate-to-severe RV dysfunction, and (5) sustained ventricular or atrial arrhythmias [1,2,14]. Since the universal definitions of severe RV dilatation and moderate-to-severe RV dysfunction are lacking, we did not use pre-specified criteria for RV dilatation and RV dysfunction. These were judged arbitrarily on the basis of available findings of imaging studies, and the judgement considered the contemporary guidelines, recommendations, and our own experience.

Percutaneous treatment was offered to patients with indication/indications for PVR fulfilling criteria for percutaneous pulmonary valve implantation (PPVI) i.e. those with a high probability of suitable landing zone for the valve (based on non-invasive imaging and/or cardiac catheterization) and no risk of coronary artery compression [15,16]. The remaining ones were referred for surgery. The presence of an RVOT patch per se was not a contraindication for PPVI [17].

**Statistical analysis**

All variables were presented as mean ± standard deviation (SD) or as median accompanied by interquartile range (IQR), as appropriate. Normality was tested with the use of the Kolmogorov-Smirnov test. Continuous variables were compared by using the Student t test or
the Mann-Whitney test, where appropriate. Categorical variables were compared with the use of χ² test or the Fisher exact test, as appropriate.

Receiver operating characteristics curve (ROC) analysis was used to test the ability of various parameters to identify patients with the need for PVR. We selected parameters with acceptable discrimination (area under the curve [AUC] ≥ 0.70) and applied the Cox proportional-hazards regression to determine whether any of these parameters were independent predictors. Additionally, binary analyses were performed using the cut-off values derived from ROC data.

The Kaplan-Meier curves were constructed comparing groups above and below the optimal ROC analysis-based threshold (parameters with acceptable discrimination on ROC analyses were used). Additionally, considering the previously published data indicating the low likelihood of the normalization of RV size as soon as RVEDV exceeds a certain threshold (>170 mL/m², >168 mL/m², >163 mL/m², >160 mL/m²) [6-8], we generated the survival curves for RVEDV at these threshold levels.

A two-sided P-value <0.05 was considered statistically significant. All statistical analyses were performed with MedCalc 12.1.4.0 (MedCalc, Mariakerke, Belgium) statistical software.

RESULTS

Two hundred and nine patients after TOF repair underwent CMR study in the analysed period. Flow chart demonstrating patients’ selection for the study is presented in Figure 1. The final analysis encompassed 61 patients. Table 1 presents the baseline characteristics of the patients who were treated conservatively and those referred for PPVI or surgical PVR.

PVR/PPVI

During the follow-up, 25 patients (41%) were referred for either PPVI or surgical PVR due to the following reasons: development of symptoms (n = 7), reduced exercise capacity on
cardiopulmonary exercise test (n = 13), progressive or severe RV dilatation with impaired RV systolic function (n = 4), sustained ventricular arrhythmias (n = 1). PPVI was attempted in 14 patients: (1) in 9 patients balloon sizing and cardiac catheterization revealed lack of a suitable anchoring site and the valve implantation was abandoned; (2) in 2 patients a bare metal stent was implanted with subsequent implantation of an Edwards-Sapien valve (a two-stage procedure), (3) one patient underwent stent implantation and an Edwards-Sapien valve implantation at the same procedure, (4) one patient underwent a Melody valve implantation with pre-stenting performed at the same procedure, (5) in one patient pre-stenting was performed but the stent migrated into a branch pulmonary artery during the introduction of the valve into RVOT, and the patient underwent surgical removal with a simultaneous homograft implantation. The remaining patients (n = 11) were referred for surgical treatment with homograft implantation. The mean time from the CMR study to the intervention was 21.4 ± 13.7 months.

**Factors associated with the need for PVR/PPVI**

ROC analyses revealed that the RV/LV ratio and PRF demonstrated acceptable discriminatory capacity to differentiate patients with the need for PVR/PPVI from those treated conservatively (Table 2). Neither RVEDV nor RVEF showed any association with the need for PVR (AUC = 0.63, 95% confidence interval = 0.49–0.75, \( P = 0.08 \) and AUC = 0.61, 95% confidence interval = 0.48–0.72, \( P = 0.14 \), respectively). The remaining parameters had either poor discriminatory ability or no discriminatory ability, and were not included in further analyses.

The results of the Cox proportional-hazards regression are presented in Table 3. Univariate analyses revealed that the RV/LV ratio and PRF were associated with the outcome. In multivariate analysis, PRF did not prove to be an independent predictor of the need for
PVR/PPVI either as a continuous or as a binary variable. The only independent predictor was the RV/LV ratio.

**Freedom from PVR/PPVI**

The Kaplan-Meier analysis showed that the ROC-based cut-off values of both the RV/LV ratio and PRF provided good separation of survival curves (Figure 3A–3D). We combined these two parameters and created the following subgroups: (1) patients with the RV/LV ratio \(\leq 2.4\) and PRF \(\leq 33\%\) (n = 25), (2) patients with the RV/LV ratio and PRF \(>33\%\) (n = 26), and (3) patients with the RV/LV ratio \(>2.4\) and PRF \(>33\%\) (n = 10). There were no patients with the RV/LV ratio \(>2.4\) and PRF \(\leq 33\%\) (i.e. all patients with the RV/LV ratio \(>2.4\) had PRF \(>33\%\)). The combination of the RV/LV ratio and PRF provided significant discrimination (Figure 3C, \(P = 0.0006\) by log-rank test for trend). Only 5 patients with the RV/LV ratio \(\leq 2.4\) and PRF \(\leq 33\%\) underwent PVR/PPVI (20%). On the other hand, 9 patients (90%) with the RV/LV ratio \(>2.4\) and PRF \(>33\%\) demonstrated the need for PVR/PPVI.

To avoid the potential bias caused by referring for CMR patients in whom PVR/PPVI had already been planned, we restricted the analysis to patients with PVR/PPVI performed at least 2 months after CMR (n = 54) and obtained similar results (survival proportion: 0.79 vs 0.37 vs 0.13, respectively for the described above subgroups, \(P = 0.0002\) by log-rank test for trend, Figure 3D).

The Kaplan-Meier analyses using the previously published thresholds of RVEDV indicating on the likelihood of irreversible RV dilatation, revealed no association with the outcome in any analyses (by log-rank test: \(P = 0.97\) for a threshold \(>170\) mL/m\(^2\), \(P = 0.53\) for a threshold \(>168\) mL/m\(^2\), \(P = 0.31\) for a threshold \(>163\) mL/m\(^2\), \(P = 0.17\) for a threshold \(>160\) mL/m\(^2\)).
DISCUSSION

Optimal timing for PVR in asymptomatic patients with repaired TOF remains unknown although some studies indicate certain thresholds of RV parameters beyond which PVR might be suboptimal in terms of RV size normalization and preservation of RV function [1,2, 6–9, 18-20]. The results of our study demonstrate the potential clinical usefulness of CMR variables, namely the RV/LV ratio and PRF, in asymptomatic patients with isolated PR after TOF repair. These parameters showed a significant association with the need for future PVR/PPVI in this population. Therefore, they might be used as a guide for optimal timing for PVR. This, however, needs to be confirmed in prospective studies.

By using the Cox proportional-hazards regression, we proved that the RV/LV ratio was the only independent predictor of the need for PVR/PPVI in this population. Additionally, since the Kaplan-Meier curves are better for time-dependent events, we checked the association with the future PVR/PPVI with the use of survival curves, and demonstrated that also PRF had a predictive value.

The RV/LV ratio provides a broad spectrum of information on the impact of the PR on the heart. It reflects not only RV dilatation but also adverse consequences for the left ventricle (compression – LVEDV in the PVR/PPVI group was slightly smaller than in the conservative treatment group and of borderline statistical significance – \( P = 0.057 \)), and better than RVEDV corresponds to PR severity [11]. Thus, since the decision about performing PVR in patients after TOF repair is multifactorial, the RV/LV ratio seems to be useful in this situation. Normal values of the RV/LV ratio are about 1.15 [21-22], and the value of 2.0 has been proposed as a cut-off for severe RV dilatation [23-24]. In our study, the RV/LV ratio >2.4 showed 100% specificity and positive predictive value for identifying patients who required PVR/PPVI during follow-up, i.e. all patients with the RV/LV ratio >2.4 progressed to intervention (Figure 2). The RV/LV ratio had, however, poor sensitivity. This drawback
could be at least partially reduced by combining the RV/LV ratio with PRF which at a cut-off of 33% showed a sensitivity of 80%. The combination of the RV/LV ratio and PRF provided improved discrimination when compared to either of the parameters alone (Figure 3C and 3D).

The universe definition of the severity of PR derived from CMR is lacking. Although many researchers use the threshold of 20% as a cut-off distinguishing significant from insignificant PR, higher thresholds (e.g. >25%, >35%, >40%) are used for defining severe PR [11,12,24-29]. Additionally, it has been suggested that PRV indexed for body surface area may better reflect the impact of volume load on RV than PRF does, which makes determination of PR severity on the basis of CMR parameters even more confusing [26]. We demonstrated that PRF >33% provided an acceptable discriminatory ability to distinguish between patients with the need for PVR/PPVI and the remaining ones. This may help guide therapeutic decisions in this population.

Several limitations merit consideration. First, a relatively small sample size needs to be taken into consideration. However, the strength of our study is the fact that we included a highly selected population. To avoid altering the decision on performing PVR/PPVI by the factors other than PR and its consequences, we excluded patients with residual ventricular septal defect, peak RVOT gradient ≥30 mmHg, or at least moderate tricuspid regurgitation. Secondly, like all observational non-randomized studies, our findings need to be interpreted with a certain degree of caution. Ideally, the potential benefits of incorporating CMR-based parameters in clinical-decision making should be confirmed in a randomized prospective study. However, performing such a study in patients with repaired TOF is challenging due to various reasons, and only large multicentre trials have a potential to clearly elucidate this issue. Finally, restrictive RV physiology affects right ventricular size in patients with PR. Thus, we cannot exclude influence of this factor on RV size.
In contrast to asymptomatic patients with aortic regurgitation in whom precise indications for surgery are established in terms of excessive LV dilatation and LV dysfunction with cut-off values given for these parameters, in asymptomatic patients with PR such categorical approach is limited and mainly descriptive indications are given (i.e. moderate-to-severe or progressive RV dilatation, moderate-to-severe RV dysfunction) [1,2]. Current European recommendations on performing PVR in asymptomatic patients after TOF repair do not give any cut-off value indicating the need for intervention due to RV dilatation or dysfunction leaving place for the arbitrary decision of treating physician/physicians [1]. Thus, we did not utilize any specific thresholds for RV dilatation and impaired RV function. In our study, as in a normal clinical scenario, all heart team members had full access to CMR data. This might have caused some bias and referring the patient for PVR/PPVI as soon as RVEDV exceeds a certain threshold of RV volume when no normalization of RV size should be expected [6-8]. However, the Kaplan-Meier curves did not show differences in freedom from PVR/PPVI in groups stratified according to these thresholds. Additionally, the bias was limited by making the decision on performing PVR/PPVI by a consensus of heart team members with experience in congenital heart diseases. Nevertheless, some bias cannot be excluded.

We demonstrated that the RV/LV ratio and PRF had a significant association with the need for PVR/PPVI in asymptomatic patients with isolated moderate-to-severe PR after TOF repair. However, our findings may be hampered by the retrospective design of the study and the limited number of patients included. Further studies are required to elucidate the potential clinical value of these parameters in deciding about early intervention for pulmonary incompetence in this population.
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Table 1. Baseline characteristics of the study population

| Parameter                        | Whole cohort | Conservative treatment | PVR/PPVI | P-value (conservative treatment vs PVR/PPVI) |
|----------------------------------|--------------|------------------------|----------|---------------------------------------------|
|                                 | n = 61       | n = 36                 | n = 25   |                                              |
| Males                            | 47 (77%)     | 29 (81%)               | 18 (72%) | 0.78                                        |
| Age at CMR study (years)         | 22.5 (18.8-25.3) | 24.3 ± 7.9             | 22.0 ± 3.2 | 0.11                                        |
| Age at TOF repair (years)        | 3.3 (2.2-4.6) | 3.6 (2.3-6.0)          | 3.0 (1.9-3.9) | 0.09                                        |
| Time between TOF repair and CMR study (years) | 18.7 ± 3.7 | 18.5 ± 4.0 | 19.0 ± 3.2 | 0.57                                        |
| Previous palliative shunt        | 19 (31%)     | 11 (31%)               | 8 (32%)  | 0.87                                        |
| Type of TOF repair               |              |                        |          |                                              |
| Patch                            | 43 (71%)     | 20 (55%)               | 23 (92%) | 0.003                                       |
| Conduit                          | 2 (3%)       | 2 (6%)                 | 0 (0%)   | 0.50                                        |
| Details unknown                  | 16 (26%)     | 14 (39%)               | 2 (8%)   | 0.008                                       |
| RVEDV (mL/m²)                    | 172.8 ± 38.6 | 163.7 ± 30.5           | 186.1 ± 45.3 | 0.04                                        |
| RVESV (mL/m²)                    | 93.6 ± 26.8  | 87.4 ± 23.4            | 102.6 ± 29.3 | 0.03                                        |
| RVSV (mL/m²)                     | 79.2 ± 16.2  | 76.3 ± 13.7            | 83.5 ± 18.8 | 0.09                                        |
| Parameter                  | Mean ± SD | Median (IQR) | p-value |
|----------------------------|-----------|--------------|---------|
| RVEF (%)                   | 46.3 ± 6.0| 47.2 ± 6.7   | 45.2 ± 4.9 | 0.22 |
| Corrected RVEF (%)         | 27.5 ± 6.3| 29.2 ± 6.1   | 24.9 ± 5.8 | 0.008|
| RVM (g/m²)                 | 30.1 ± 7.2| 29.1 ± 7.5   | 31.4 ± 6.8 | 0.22 |
| LVEDV (mL/m²)              | 86.3 ± 15.6| 89.5 ± 16.7 | 81.8 ± 12.9 | 0.057|
| LVESV (mL/m²)              | 38.7 ± 10.3| 40.1 ± 11.2 | 36.8 ± 8.6  | 0.22 |
| LVSV (mL/m²)               | 47.6 ± 7.9 | 49.4 ± 8.2   | 45.0 ± 6.7  | 0.03 |
| LVEF (%)                   | 55.6 ± 5.9 | 55.8 ± 6.3   | 55.3 ± 5.2  | 0.77 |
| LVM (g/m²)                 | 54.5 ± 12.3| 55.1 ± 12.0  | 52.4 ± 11.4 | 0.38 |
| RV/LV ratio                | 2.04 ± 0.48| 1.86 ± 0.32  | 2.30 ± 0.54 | 0.0008|
| PRF (%)                    | 36.6 ± 11.9| 32.8 ± 11.5  | 41.8 ± 10.6 | 0.003|
| PRV (mL/m²)                | 28.2 ± 13.7| 24.2 ± 11.8  | 33.9 ± 14.5 | 0.006|

Data are expressed as mean ± standard deviation, median (inter-quartile range) or number of patients (percentage).

CMR, cardiac magnetic resonance; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; LVSV, left ventricular stroke volume; PPVI, percutaneous pulmonary valve implantation; PRF, pulmonary regurgitation fraction; PRV, pulmonary regurgitation volume; PVR, pulmonary valve replacement; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVM, right ventricular mass; RVSV, right ventricular stroke volume; RV/LV, right ventricular volume to left ventricular volume; TOF, tetralogy of Fallot.
Table 2. Receiver operating characteristic analyses. The ability of CMR parameters to discriminate patients with the need for PVR/PPVI from those treated conservatively is presented.

| Parameter       | AUC   | Threshold | P-value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|-----------------|-------|-----------|---------|-----------------|-----------------|---------|---------|
| RV/LV ratio     | 0.74  | > 2.4     | 0.001   | 36 (18-58)      | 100 (90-100)    | 100 (66-100) | 70 (55-81) |
| PRF (%)         | 0.71  | > 33      | 0.002   | 80 (59-93)      | 56 (38-72)      | 56 (38-72) | 80 (59-93) |

Numbers in parentheses are 95% confidence intervals.

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; PRF, pulmonary regurgitation fraction; RV/LV, right ventricular volume to left ventricular volume
Table 3. Cox proportional-hazards regression analyses. Variables with acceptable discriminatory ability on ROC analysis were included.

| Variable   | Univariate Analysis | Multivariate Analysis | Univariate Analysis | Multivariate Analysis |
|------------|---------------------|-----------------------|---------------------|-----------------------|
|            | Hazard Ratio        | $P$-value             | Hazard Ratio        | $P$-value             | Hazard Ratio        | $P$-value             |
| RV/LV ratio| 5.0                 | 0.0002                | 5.0                 | 0.0002                | 4.3                 | 0.001                |
|            | (2.3-11.1)          |                       | (2.3-11.1)          |                       | (1.9-9.9)           |                      |
| PRF        | 1.05                | 0.01                  | …                   | …                     | 2.8                 | 0.02                 |
|            | (1.01-1.09)         |                       |                      |                       | (1.07-7.6)          |                      |

Numbers in parentheses are 95% confidence intervals.

Binary analyses compared patients above and below the optimal ROC analysis-based threshold.

Abbreviations — see Table 1
Figure 1. Flow chart demonstrating patients’ selection in the study.

CMR, cardiac magnetic resonance; PR, pulmonary regurgitation; RVOT, right ventricular outflow tract; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
Figure 2. Scatterplots of the RV/LV ratio (A) and PRF (B) in the conservative treatment and PVR/PPVI groups. Solid lines indicate the optimal thresholds for identifying patients with the need for PVR/PPVI.

Abbreviations — see Table 1
Figure 3. The Kaplan-Meier curves for survival without PVR/PPVI

A. Stratified by the RV/LV ratio.

B. Stratified by PRF.

C. Stratified by both the RV/LV ratio and PRF.
D. Stratified by both the RV/LV ratio and PRF in a population restricted to patients with PVR/PPVI performed at least 2 months after CMR.

Abbreviations — see Table 1