Original Research

Impact of Right Ventricular Pressure Load After Repair of Tetralogy of Fallot

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BACKGROUND: Right ventricular outflow tract (RVOT) stenosis after repair of tetralogy of Fallot has been linked with favorable right ventricular remodeling but adverse outcomes. The aim of our study was to assess the hemodynamic impact and prognostic relevance of right ventricular pressure load in this population.

METHODS AND RESULTS: A total of 296 patients with repaired tetralogy of Fallot (mean age, 17.8±7.9 years) were included in a prospective cardiovascular magnetic resonance multicenter study. Myocardial strain was quantified by feature tracking technique at study entry. Follow-up, including the need for pulmonary valve replacement, was assessed. The combined end point consisted of ventricular tachycardia and cardiac death. A higher echocardiographic RVOT peak gradient was significantly associated with smaller right ventricular volumes and less pulmonary regurgitation, but lower biventricular longitudinal strain. During a follow-up of 10.1 (0.1–12.9) years, the primary end point was reached in 19 of 296 patients (cardiac death, n=6; sustained ventricular tachycardia, n=2; and nonsustained ventricular tachycardia, n=11). A higher RVOT gradient was associated with the combined outcome (hazard ratio [HR], 1.03; 95% CI, 1.00–1.06; P=0.026), and a cutoff gradient of ≥25 mm Hg was predictive for cardiovascular events (HR, 3.69; 95% CI, 1.47–9.27; P=0.005). In patients with pulmonary regurgitation ≥25%, a mild residual RVOT gradient (15–30 mm Hg) was not associated with a lower risk for pulmonary valve replacement.

CONCLUSIONS: Higher RVOT gradients were associated with less pulmonary regurgitation and smaller right ventricular dimensions but were related to reduced biventricular strain and emerged as univariate predictors of adverse events. Mild residual pressure gradients did not protect from pulmonary valve replacement. These results may have implications for the indication for RVOT reintervention in this population.

Key Words: magnetic resonance imaging ▪ prognosis ▪ right ventricular pressure overload ▪ strain ▪ tetralogy of Fallot

Following surgical repair of tetralogy of Fallot (TOF), pulmonary regurgitation (PR) frequently emerges as the predominant residual lesion causing progressive right ventricular (RV) enlargement, functional impairment, and, potentially, sudden cardiac death.1 Surgical management of patients after TOF repair has therefore shifted toward a pulmonary valve-sparing repair technique with the aim of preserving RV integrity.2 Subsequently, some degree of residual pulmonary stenosis is typically accepted after repair and has been shown to have beneficial effects on the described adverse RV remodeling process by reducing PR and RV enlargement without compromising RV function.3–5 Furthermore, mild residual RV outflow tract (RVOT) gradients may also postpone the need for pulmonary valve replacement (PVR).6,7 In contrast, recent data from several studies demonstrated elevated RV pressure as an independent predictor for adverse
outcome. These apparently paradoxical findings suggest that the effect of RV pressure load on biventricular remodeling in patients with repaired TOF is not yet sufficiently characterized and that the underlying pathophysiological mechanisms that link increased RV pressures with unfavorable outcomes are unclear. Accordingly, the aim of this study was to assess the hemodynamic impact and prognostic relevance of RV pressure load in a larger cohort of patients with repaired TOF.

**METHODS**

The data that support the findings of this study are available from the corresponding author on reasonable request.

**Study Population**

Patients with repaired TOF were enrolled in a prospective nationwide study by the German Competence Network for Congenital Heart Defects between 2003 and 2009 (Follow Up of Post-Repair Tetralogy of Fallot; https://www.clinicaltrials.gov; unique identifier, NCT00266188). This multicenter study included patients with repaired TOF, aged >8 years, from 14 German sites undergoing a standardized protocol, including the collection of demographic and clinical data (including echocardiography) and the assessment of cardiopulmonary exercise testing and cardiovascular magnetic resonance (CMR) imaging, as published.11,12

For the current study, patients with cardiopulmonary exercise testing data (peak oxygen uptake and percentage predicted and peak heart rate), echocardiographic assessment of the peak systolic RVOT gradient, and a comprehensive initial CMR examination (including biventricular volumetry and quantification of pulmonary regurgitation fraction using phase-contrast flow measurements) were considered for further analysis. These examinations were performed within a close time interval at study entrance, and the patients were then prospectively followed up until July 2018. Data on initial postrepair RVOT gradients as well as longitudinal hemodynamic changes were not assessed.

Appropriate 4-chamber and midventricular short-axis cine loops of study entry CMR examinations were extracted from the central database of the Competence Network for Congenital Heart Defects. CMR feature tracking analysis (TomTec Imaging Systems, Unterschleissheim, Germany) of both ventricles was performed to assess peak global longitudinal, circumferential, and radial strain values, the early diastolic strain rate, and interventricular synchrony, as described previously.13

Information on follow-up data, including the occurrence of predefined adverse events and PVR procedures (both surgical and transcatheter valve implantation), was available through the infrastructure of the Competence Network for Congenital Heart Defects as all patients were also separately enrolled in the national registry database for congenital heart defects. These data include survival information as well as up-to-date medical reports obtained regularly from the physicians treating the patients. The study was approved by all ethics committees of the participating centers. Informed written consent was obtained from all patients or their caretakers.

**Statistical Analysis**

All continuous variables were tested for normality using the D’Agostino-Pearson omnibus test and are presented as a mean with SD or median and range. Comparisons between the patient groups with versus without adverse events were made with the Student t test, the Mann-Whitney U test, or the Fisher exact test, as appropriate. The Pearson correlation coefficient was used to analyze simple linear relationships between different variables. Outcome analyses were based on freedom from PVR and the primary composite end point, including cardiac death, successful resuscitation, and documented episodes of ventricular

**CLINICAL PERSPECTIVE**

**What Is New?**

- In patients after repair of tetralogy of Fallot, higher right ventricular outflow tract gradients were related to reduced biventricular strain and emerged as univariate predictors of adverse events.
- Mild residual pressure gradients did not reduce the risk for later pulmonary valve replacement.

**What Are the Clinical Implications?**

- Our findings may affect the timing and indication of pulmonary valve replacement procedures in patients after repair of tetralogy of Fallot.
- Prospective studies will need to determine whether pulmonary valve replacement performed at lower levels of right ventricular pressure load will be associated with favorable outcomes.

**Nonstandard Abbreviations and Acronyms**

| PR | pulmonary regurgitation |
|----|-------------------------|
| TOF | tetralogy of Fallot |
tachycardia (either sustained or nonsustained) that occurred during the follow-up time from the CMR study. The relationship between demographic, clinical, and CMR variables and outcomes was investigated by univariable and bivariable (including the peak RVOT gradient and one other significant parameter on univariable testing) Cox proportional-hazard analysis (hazard ratio [HR] with 95% CI). To further assess the prognostic impact of residual RV pressure load, the study population was divided into 2 groups according to a cutoff RVOT gradient of <25 and ≥25 mm Hg. This threshold emerged from previous studies that assessed the relevance of residual RVOT stenosis in patients after repair of TOF. The log-rank (Mantel-Cox) test was performed to compare the risk for PVR in subgroups with different degrees of RV pressure and/or volume overload. Analysis was performed using GraphPad (San Diego, CA) and SPSS (version 25.0; IBM Inc, Armonk, NY) statistical software packages. For all analyses, a 2-tailed \( P < 0.05 \) was used as the criterion for statistical significance.

**RESULTS**

**Patient Characteristics and CMR Data**

From the total population of 407 patients with repaired TOF enrolled in the multicenter study, 337 had a suitable data set for the intended analysis that included echocardiographic peak RVOT gradient, a comprehensive CMR analysis, and a completed cardiopulmonary exercise testing examination (Figure 1). A comparison between the analysis sample and those patients excluded is displayed in Table S1. In 301 of these 337 patients (89%), longitudinal follow-up data were available (in 36 patients, no follow-up data could be obtained within the national database of the registry for congenital heart disease in Germany). For the outcome analysis, another 5 patients were excluded as these patients already exhibited one of the predefined end points (nonsustained ventricular tachycardia [VT] in 3 patients and sustained VT in 2 patients) and were subsequently treated with specific antiarrhythmic drug therapy and/or received PVR. Finally, 296 patients who had a CMR study at a mean age of 17.8±7.9 years (range, 7.0–58.0 years) were included as these patients already exhibited one of the predefined end points (nonsustained ventricular tachycardia [VT] in 3 patients and sustained VT in 2 patients) and were subsequently treated with specific antiarrhythmic drug therapy and/or received PVR. Finally, 296 patients who had a CMR study at a mean age of 17.8±7.9 years (range, 7.0–58.0 years) were included in the outcome analysis. The mean peak echocardiographic RVOT gradient was 20.7±14.9 mm Hg (median, 16 mm Hg; range, 2–83 mm Hg). For details, please see Table 1.

**Correlations**

Peak RVOT gradient was significantly associated with smaller RV volumes \( (r=−0.16; \ P=0.004) \) and less PR \( (r=−0.12; \ P=0.026) \), but lower RV \( (r=−0.23; \ P=0.0004) \) and left ventricular (LV) longitudinal systolic strain \( (r=−0.15; \ P=0.016) \), and lower early diastolic strain rate \( (r=−0.17; \ P=0.01) \) and \( r=−0.22 \ (P=0.0006) \); Figure 2). No significant relationships were found between RVOT gradient and RV ejection fraction (RVEF), RV mass, and RV mass/volume ratio. LV dimensions and LV ejection fraction were not related to the RVOT gradient. Although not of statistical significance, a trend toward reduced exercise capacity (both peak oxygen uptake and oxygen uptake at ventilator anaerobic threshold) was observed with increasing RVOT gradients.

**Prognostic Relevance of RVOT Gradient**

During a median follow-up of 10.1 (range, 0.1–12.9) years, the primary end point was reached in 19 of 296 patients, occurring at a median time of 10.1 (range, 0.6–12.9) years after the CMR study (cardiac death, \( n=6; \) sustained VT, \( n=2; \) and nonsustained VT, \( n=11 \)). Using univariable Cox-regression analysis, a higher RVOT gradient was significantly associated with the combined outcome (HR, 1.03; 95% CI, 1.01–1.06; \( P=0.006 \)). Other significant predictors were New York Heart Association functional class >1, peak oxygen uptake, PVR during follow-up, right ventricular end-systolic volume (RVESVi), left ventricular end-diastolic volume (LVEDVi), left ventricular end-systolic volume (LVEDVi), RV longitudinal strain, RV circumferential strain, LV circumferential strain, and LV radial strain (Table 2).

A peak RVOT gradient of ≥25 mm Hg was associated with a >3-fold increase in adverse cardiovascular events (HR, 3.69; 95% CI, 1.47–9.27; \( P=0.005 \)) (Figure 3). A subgroup analysis according to a peak RVOT gradient of <25 and ≥25 mm Hg and the degree of PR (<25% and ≥25%) is displayed in Figure S1. Patients with moderate PR and a peak RVOT gradient ≥25 mm Hg demonstrated significantly more adverse events than patients with moderate PR and a peak RVOT gradient <25 mm Hg \( (P<0.001) \). In patients with severe PR ≥25%, RVOT gradients >25 or <25 mm Hg led to no significant difference \( (P=0.38) \).

Instead of multivariable testing that may not yield reliable results given the limited number of adverse events ("overfitting of the model"), bivariable testing was performed to elucidate the relationship between the peak RVOT and other parameters found to be significant on univariate analysis (Table 3). All tested parameters remained independent predictors, except of the paired testing with RV longitudinal strain, where the RVOT gradient reached a level of significance of \( P=0.05 \).

A second univariable Cox proportional-hazard analysis was performed that only considered death and sustained VT as adverse events \( (N=8) \) (Table S2). Peak RVOT gradient remained a significant predictor for adverse events (HR, 1.04; 95% CI, 1.00–1.07; \( P=0.046 \)). Comparison between patients with <25 and ≥25 mm Hg RVOT gradient showed a clear trend toward a worse outcome for patients with higher RVOT gradient ( Cochran-Armitage trend test, \( P=0.026 \)).
≥25 mm Hg RVOT gradient revealed a significant and much higher risk for patients with higher gradients (HR, 17.9; 95% CI, 2.19–146.2; P=0.007).

**Role of Peak RVOT Gradient in the Need for PVR**

Data on PVR procedures during follow-up were available in 292 of the 296 patients (definite information on PVR was not available in 4 patients). PVR was performed in 119 patients (41%) at a median of 3.0 (range, 0.1–12.3) years after the CMR examination. Using univariable Cox-regression analysis, a higher RVOT gradient was significantly associated with the need for PVR (HR, 1.02; 95% CI, 1.01–1.03; P=0.002). Other significant factors predictive for PVR were initial palliation, poorer New York Heart Association
### Table 1. Study Population With Initial Demographic, Clinical, and CMR Imaging Data

| Parameter                                      | All patients (N=296) | Patients without event (N=277) | Patients with event (N=19) |
|------------------------------------------------|----------------------|-------------------------------|---------------------------|
| **Demographics**                               |                      |                               |                           |
| Diagnosis, n (%)                               | 283 (96)             | 265 (96)                      | 18 (95)                   |
| TOF/pulmonary stenosis                         | 260 (92)             | 243 (92)                      | 17 (94)                   |
| TOF/PA                                         | 23 (8)               | 22 (8)                        | 1 (6)                     |
| Age at CMR, y                                  | 16.0 (7.0–58.0)      | 16.0 (7.0–58.0)               | 16.0 (8.0–44.0)           |
| Age at corrective surgery, y                   | 1.0 (0.1–28.0)       | 1.0 (0.1–28.0)                | 1.0 (0.1–19.0)            |
| Type of repair, n (%)                          |                      |                               |                           |
| Data available                                 | 258 (87)             | 240 (87)                      | 18 (95)                   |
| Without TAP                                    | 143 (55)             | 131 (55)                      | 12 (67)                   |
| TAP                                            | 62 (24)              | 58 (24)                       | 4 (22)                    |
| TAP and pulmonary artery plasty                | 53 (21)              | 51 (21)                       | 2 (11)                    |
| Time from repair, y                            | 14 (6–48)            | 14 (6–48)                     | 15 (8–35)                 |
| Follow-up, y                                   | 10.1 (0.1–12.9)      | 10.1 (0.1–12.9)               | 10.1 (0.8–12.9)           |
| PVR during follow-up, n/total (%)              | 119/292 (41)         | 105/274 (38)                  | 14/16 (78)                |
| **Clinical status and history**                |                      |                               |                           |
| Initial palliation, n/total (%)                | 67/282 (24)          | 60/264 (24)                   | 7/18 (39)                 |
| Previous PVR, n/total (%)                      | 70/296 (24)          | 62/277 (22)                   | 8/19 (42)                 |
| NYHA>class I, n/total (%)                      | 96/296 (32)          | 86/277 (31)                   | 10/19 (52)                |
| 12-Lead ECG: QRS duration, ms                  | 147±22               | 147±22                        | 146±26                    |
| **Cardiopulmonary exercise test**              |                      |                               |                           |
| Peak VO₂ at VAT, mL/min per kg                 | 23.8±7.5             | 24.0±7.4                      | 21.6±9.0                  |
| Peak VO₂, mL/min per kg                        | 31.1±8.4             | 31.3±8.2                      | 26.4±10.7                 |
| Peak heart rate, /min                          | 172 (79–204)         | 172 (79–204)                  | 170 (89–197)              |
| **Echocardiography**                           |                      |                               |                           |
| Peak RVOT gradient, mm Hg                      | 20.7±14.9            | 20.0±14.3                     | 29.9±19.3                 |
| Tricuspid valve regurgitation>moderate, n/total (%) | 22/211 (10)       | 19/195 (10)                   | 3/16 (19)                 |
| **CMR study**                                  |                      |                               |                           |
| RVEDVi, mL/m²                                   | 116 (67–242)         | 115 (67–242)                  | 119 (84–224)              |
| RVESVi, mL/m²                                   | 57 (20–186)          | 56 (20–161)                   | 66 (26–186)               |
| RVSVI, mL/m²                                    | 60±16                | 60±16                         | 60±13                     |
| RVEF, %                                        | 51±9                 | 51±9                          | 47±12                     |
| PR, %                                          | 27 (0–65)            | 27 (0–65)                     | 28 (1–54)                 |
| RV mass, g/m²                                   | 33 (10–103)          | 33 (10–103)                   | 35 (24–71)                |
| RV mass/volume ratio                           | 0.29 (0.08–0.74)     | 0.22 (0.08–0.74)              | 0.30 (0.16–0.66)          |
| LVEDVi, mL/m²                                   | 82 (43–195)          | 81 (43–126)                   | 87 (60–195)               |
| LVESVi, mL/m²                                   | 34 (17–166)          | 34 (17–91)                    | 37 (22–166)               |
| LVSVI, mL/m²                                    | 47 (23–87)           | 47 (23–87)                    | 47 (28–68)                |
| LVEF, %                                        | 58 (15–74)           | 58 (20–74)                    | 56 (15–69)                |
| LV mass, g/m²                                   | 54 (30–127)          | 54 (30–109)                   | 55 (33–127)               |
| LV mass/volume ratio                           | 0.69±0.18            | 0.69±0.18                     | 0.69±0.20                 |
| **Feature tracking analysis**                  |                      |                               |                           |
| RV-LS, %                                       | −12.9±4.6            | −13.1±4.5                     | −9.9±5.0                  |
| RV-CS, %                                       | −15.2±4.1            | −15.4±4.0                     | −13.3±5.1                 |
| LV-LS, %                                       | −13.8±5.0            | −14.0±4.9                     | −12.1±6.5                 |
| LV-CS, %                                       | −20.7±4.8            | −21.0±4.3                     | −16.9±7.8                 |

(Continued)
functional class, increased RV volumes and RV mass, PR severity, as well as lower RVEF and LV ejection fraction (Table 3).

To assess the impact of a mild residual RVOT stenosis (peak RVOT gradient 15–30 mm Hg) on the need for PVR, this subgroup was compared with patients with no relevant gradient (<15 mm Hg) and a group of patients with moderate or severe RVOT gradient (>30 mm Hg) (Figure 4 and Table S3). The groups were further separated into patients with <25% PR and a group with ≥25% PR. In patients with ≥25% PR, the need for PVR was similar between the different RVOT stenosis subgroups. Patients with <25% PR and RVOT gradients <30 mm Hg had the lowest risk for PVR (Table 4).

**DISCUSSION**

Our study demonstrated that a higher peak RVOT gradient was associated with less PR and smaller RV volumes in patients with repaired TOF, but also negatively affected biventricular systolic and diastolic longitudinal strain at study entry, even in a relatively young study population, and emerged as a univariate predictor for adverse cardiovascular events. More important, peak RVOT pressure gradients of >25 mm Hg were associated with a >3-fold higher risk for death and ventricular tachyarrhythmia, even in this young cohort. Although it remains unclear whether the peak RVOT gradient will come out as an independent predictor of adverse outcomes in this population, the results of our study underscore the hemodynamic and prognostic relevance of mild to moderate RV pressure load in patients with repaired TOF that may also have implications for the indication and timing of RVOT reinterventions. Furthermore, our study also showed that a mild residual RVOT gradient of 15 to 30 mm Hg did not protect from later PVR in patients with significant PR.

**Hemodynamic Impact of RV Pressure Load**

Preservation of pulmonary valve competence and bi-ventricular function are primary objectives in the long-term surveillance of patients with repaired TOF. Mild to moderate residual RVOT gradients are usually well tolerated and are even supposed to have beneficial effects on exercise performance, RV enlargement, and function.3,4 The results of our study support these results in so far as increased RVOT gradients were associated with less PR and smaller RV dimensions.3–5,14,15 Other than reported in previous observations, no significant relationship was observed between exercise capacity and RV afterload.16

Remarkably, although RVEF and LV ejection fraction were not related to residual pressure load, a weak but significant inverse relationship with both RV and LV longitudinal systolic and diastolic myocardial strain/strain rate was observed. Contrary findings were published previously, showing preserved systolic RV strain values in patients with repaired TOF who presented with higher RVOT gradients.13 The underlying reason for these divergent findings remains speculative, but differences in patient demographics, such as age, surgical techniques, and reinterventions, offer potential explanations.

Although the reported simple linear correlations are not able to detect any causal relationships, it seems worth discussing potential mechanisms linking higher RV afterload with impaired RV performance. RV myocardial fibrosis is now recognized as an adverse marker for clinical outcomes in patients with repaired TOF.17 Recent CMR studies assessed diffuse myocardial fibrosis and reported lower degrees of fibrosis within the RV myocardium with increasing RVOT gradients.18 However, in a histopathological study performed at the time of PVR, Kido and colleagues found an elevated amount of RV fibrosis in patients with a higher
RV/LV pressure ratio. In fact, the CMR T1 mapping techniques applied cannot differentiate whether the observed expansion in extracellular matrix is caused by a “real” profibrotic process or is attributable to a “relative” increase caused by cardiomyocyte atrophy. Whether increased RV afterload induces reactive fibrotic remodeling of the myocardium in patients with repaired TOF therefore remains unclear, in particular where RV pressures are only mildly or moderately increased.

As a consequence of elevated RV pressure, compensatory myocardial hypertrophy occurs and promotes RV myocardial stiffness that potentially protects from progressive ventricular dilatation. This assumption is supported by the finding that diastolic RV longitudinal strain rate was associated with higher

Figure 2. Graph displaying several linear correlations between the echocardiographic (echo) peak right ventricular outflow tract (RVOT) gradient and cardiovascular magnetic resonance measures of biventricular dimensions and function as well as results from cardiopulmonary exercise testing. Higher RVOT gradients were significantly associated with smaller right ventricular end-diastolic volumes (RVEDVI) and less pulmonary regurgitation (PR) but were also related with reduced global right ventricular (RV) and left ventricular (LV) longitudinal systolic (strain) and diastolic (strain rate) deformation. No significant correlation was observed between peak RVOT gradient and exercise capacity (peak oxygen uptake [VO₂] and percentage predicted). EDSR indicates early diastolic strain rate; EF, ejection fraction; LS, longitudinal strain; and VAT, ventilator anaerobic threshold.
Table 2. Univariable Predictors of the Combined Study End Point of Cardiac Death, Successful Resuscitation, and Sustained or Nonsustained VT

| Parameter | HR   | 95% CI       | P value |
|-----------|------|--------------|---------|
| Diagnosis (TOF/PA vs TOF) | 1.10 | 0.14–8.40    | 0.93    |
| Age at CMR (y) | 1.04 | 0.99–1.08    | 0.11    |
| Age at corrective surgery (y) | 1.05 | 0.96–1.15    | 0.27    |
| Type of repair (TAP vs no TAP) | 0.63 | 0.23–1.71    | 0.37    |
| Time from repair (y) | 1.05 | 0.98–1.11    | 0.15    |
| Initial palliation (yes/no) | 2.22 | 0.74–6.63    | 0.15    |
| Previous PVR (yes/no) | 2.37 | 0.94–5.93    | 0.07    |
| PVR during follow-up (yes/no) | 3.57 | 1.15–11.1    | 0.028*  |
| NYHA class >I (yes/no) | 3.42 | 1.34–8.73    | 0.01*   |
| QRS (ms) | 0.99 | 0.97–1.01    | 0.34    |
| Peak VO2 at VAT, mL/min per kg | 0.95 | 0.88–1.01    | 0.10    |
| Peak VO2, mL/min per kg | 0.92 | 0.88–0.97    | 0.004*  |
| Peak heart rate (/min) | 0.98 | 0.97–1.00    | 0.08    |
| RVOT gradient, mm Hg | 1.03 | 1.01–1.06    | 0.006*  |
| Tricuspid valve regurgitation > moderate (yes/no) | 1.19 | 0.32–4.41    | 0.79    |
| RVEDVi, mL/m² | 1.01 | 1.00–1.03    | 0.10    |
| RVESVi, mL/m² | 1.02 | 1.00–1.04    | 0.02*   |
| RVSVi, mL/m² | 1.00 | 0.97–1.03    | 0.88    |
| RVEF, % | 0.96 | 0.92–1.01    | 0.13    |
| PR, % | 1.00 | 0.97–1.03    | 0.97    |
| RV mass, g/m² | 1.01 | 0.98–1.04    | 0.56    |
| RV mass/volume ratio | 1.21 | 0.02–66.52   | 0.93    |
| LVESVi, mL/m² | 1.04 | 1.01–1.06    | 0.001*  |
| LVEDVi, mL/m² | 1.03 | 1.02–1.05    | <0.001* |
| LVESVi, mL/m² | 1.00 | 0.95–1.06    | 0.91    |
| LVEF, % | 0.96 | 0.91–1.00    | 0.07    |
| LV mass, g/m² | 1.01 | 0.98–1.04    | 0.49    |
| LV mass/volume ratio | 0.47 | 0.03–9.16    | 0.62    |
| RV-LS, % | 1.22 | 1.07–1.39    | 0.004*  |
| RV-CS, % | 1.15 | 1.01–1.31    | 0.03*   |
| LV-LS, % | 1.07 | 0.96–1.19    | 0.24    |
| LV-CS, % | 1.16 | 1.06–1.27    | 0.002*  |
| LV-RS, % | 0.93 | 0.87–1.00    | 0.04*   |
| RV EDSR LS (1/s) | 0.78 | 0.20–3.00    | 0.71    |
| RV EDSR CS (1/s) | 0.26 | 0.05–1.47    | 0.13    |
| LV EDSR LS (1/s) | 0.93 | 0.37–2.34    | 0.88    |
| LV EDSR CS (1/s) | 0.53 | 0.17–1.69    | 0.28    |
| Interventricular dyssynchrony LS, ms | 1.01 | 1.00–1.01    | 0.16    |
| Interventricular dyssynchrony CS, ms | 0.99 | 0.97–1.01    | 0.25    |

CMR indicates cardiovascular magnetic resonance; CS, circumferential strain; EDSR, early diastolic strain rate; HR, hazard ratio; LS, longitudinal strain; LV, left ventricular; LVEDVi, indexed left ventricular end-diastolic volume; LVEF, LV ejection fraction; LVESVi, indexed left ventricular end-systolic volume; LVSVi, indexed left ventricular stroke volume; NYHA, New York Heart Association; PA, pulmonary atresia; PR, pulmonary regurgitation; PVR, pulmonary valve replacement; RS, radial strain; RV, right ventricular; RVESVi, indexed right ventricular end-diastolic volume; RVESVi, indexed right ventricular end-systolic volume; RVSVi, indexed right ventricular stroke volume; RVEF, RV ejection fraction; RVOT, RV outflow tract; TAP, transannular patch; TOF, tetralogy of Fallot; VAT, ventilator anaerobic threshold; VO2, oxygen uptake; and VT, ventricular tachycardia.

*indicates statistical significance (P<0.05).

RV Pressure Load as a Predictor of Outcome

In addition to established clinical risk factors, our study demonstrated that elevated RVOT gradients measured any time after repair emerged as univariate predictors of cardiac death and ventricular tachyarrhythmia over a long-term course. Several previous CMR studies in patients with repaired TOF identified risk factors for adverse cardiovascular events; however, RV pressure load has not been consistently analyzed in all of these studies, and where it has been included in the analysis, its prognostic relevance differs between studies.8,23,24

Our findings are in accordance with those of the multicenter INDICATOR (International Multicenter TOF Registry) study that revealed increased RV pressure as an independent risk factor.9,26 In contrast to our population, higher RV mass as well as lower LV ejection fraction were further significant predictors. To explain the different results, several differences between the INDICATOR study and our study group seem worth considering: our cohort was substantially younger (median, 16.0 versus 24.4 years), the follow-up, including adverse events, was prospectively assessed, non-sustained VT was considered as part of the composite end point, and correlations to initial exercise testing results were possible. Accordingly, our patients may potentially reflect a more contemporary cohort of TOF survivors with smaller RVs and less PR who may be affected by risk factors detected at an earlier stage.

However, RV pressure was not found to be predictive for the occurrence of VT in another CMR multicenter study.24 Nevertheless, increased RV afterload constitutes an important risk factor after repair of TOF, as recently demonstrated by Egbe and colleagues, who showed that elevated systolic RV pressure, assessed either invasively or noninvasively, was independent of death and heart transplantation.10

Another study by this group further revealed that combined indexes of RV systolic pressure and function (ie, right ventricular end-systolic volume and RVEF) better correlated with disease severity than volumetric measures alone. This finding demonstrates the importance of linking indexes of RV afterload with that of RV performance, in particular as these variables seem to be related and hold prognostic relevance. As reported in previous studies, RV systolic strain, but not RVEF, appeared to be a significant predictor in univariable testing.12,22,26,27 More important, when combined in a

pressure gradients in our population. Finally, as seen with RV myocardial strain values, a higher RVOT gradient was also negatively associated with LV longitudinal systolic and diastolic strain/strain rate, which highlights the importance of ventricular interactions in patients after repair of TOF.22
bivariable model, solely RV longitudinal strain but not peak RVOT gradient remained independently associated with the combined end point. It might therefore be possible that an increased RVOT gradient translates into unfavorable outcomes by its negative impact on RV deformation.

Table 3. Cox Proportional Hazard Analysis Using a Bivariable Model of the Parameters That Reached a Significant Level on Univariable Testing to Identify Their Prognostic Relevance in Conjunction With the Peak RVOT Gradient

| Parameter                        | HR     | 95% CI     | P value |
|---------------------------------|--------|------------|---------|
| RVOT gradient, mm Hg            | 1.03   | 1.00–1.06  | 0.025*  |
| Peak VO2 at VAT, mL/min per kg  | 0.93   | 0.88–0.98  | 0.01*   |
| RVOT gradient, mm Hg            | 1.03   | 1.00–1.06  | 0.016*  |
| LVEDVi, mL/m²                   | 1.03   | 1.01–1.05  | 0.003*  |
| RVOT gradient, mm Hg            | 1.04   | 1.00–1.06  | 0.007*  |
| LVESVi, mL/m²                   | 1.03   | 1.02–1.05  | <0.001* |
| RVOT gradient, mm Hg            | 1.03   | 1.00–1.06  | 0.05    |
| RV-LS, %                        | 1.17   | 1.02–1.35  | 0.023*  |
| RVOT gradient, mm Hg            | 1.03   | 1.00–1.06  | 0.045*  |
| LV-CS (%)                       | 1.14   | 1.04–1.24  | 0.006*  |

CS indicates circumferential strain; HR, hazard ratio; LS, longitudinal strain; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume; LVESVi, left ventricular end-systolic volume; RV, right ventricular; RVOT, RV outflow tract; VAT, ventilator anaerobic threshold; and VO₂, oxygen uptake.

*indicates statistical significance (P<0.05).
TOF. Its relevance seems to be overestimated in the presence of a pulmonary PR fraction >25%. Nevertheless, the assessment of RVOT gradient may be a more precise and reliable method compared with measuring the tricuspid valve regurgitation velocity jet, especially in patients with only mild tricuspid valve regurgitation. Serial measurements of the RVOT gradient and PR fractions both before and after CMR examination were not assessed in this study, but could potentially provide insight into the longitudinal evolution and progression of RV pressure load and its prognostic impact. Furthermore, data on changes in peak RVOT gradient and biventricular function during exercise could also add important hemodynamic information.

The overall low number of adverse events, and thus the lack of a multivariable outcome analysis together
with the inclusion of nonsustained VT as an end point, limits the statistical power of the outcome analysis. However, even when only patients with death and sustained VT were considered in the outcome analysis, a higher RVOT gradient remained of prognostic significance. A total of 27% of patients from the original data set were excluded for lack of long-term follow-up data; therefore, a certain selection bias may be present (for details, see Table S1). However, the observed differences to our understanding should not have a critical effect on the results of our analysis and its drawn conclusions as the main parameters, such as age at repair, type of repair, amount of residual stenosis/regurgitation, and exercise tolerance, were not statistically significantly different. As mentioned, the inclusion of patients with Fallot-type pulmonary atresia (although not identified as a risk factor) as well as patients with previous PVR affects the character of the study population and needs to be considered when comparing our results with those of other studies with cohorts consisting primarily of patients with a “native” RVOT. The potential risk of PVR during follow-up needs to be considered in view of the significant higher proportion of PVR procedures in the group with an adverse outcome. It remains unclear whether these events were related (at least in some part) to the surgical procedures or may rather reflect disease severity before PVR.

**CONCLUSIONS**

Although higher peak RVOT gradients were associated with less PR and smaller RV dimensions, an inverse relationship with reduced systolic and diastolic biventricular longitudinal strain was present. Increased RVOT gradients also emerged as univariate predictors of adverse cardiovascular events in the long-term course. Mildly increased pressure gradients had no protective effect on later PVR procedures. These results may have implications for the indication and timing of RVOT reintervention in patients with repaired TOF. An optimal degree of pressure load, which ensures a protective effect on RV remodeling without compromising ventricular function and outcome, still needs to be determined.

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Disclosures
None.

Supplemental Material
Tables S1–S3
Figure S1
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Table S1. Comparison between the analysis sample for the current study and those patients that were excluded from the original data set

| Parameter                              | Patients included | Patients excluded | p value |
|----------------------------------------|-------------------|-------------------|---------|
| **Demographics**                       |                   |                   |         |
| Diagnosis, n (%)                       |                   |                   |         |
| Data available                         | 283 (96)          | 106 (95)          | 0.02    |
| TOF / pulmonary stenosis               | 260 (92)          | 90 (85)           |         |
| TOF /PA                                | 23 (8)            | 16 (15)           |         |
| Age at CMR (years)                     | 16.0 (7.0-58.0)   | 16.0 (6.0-53.0)   | 0.69    |
| Age at corrective surgery (years)      | 1.0 (0.1-28.0)    | 2.0 (0.1-19.0)    | 0.05    |
| Type of repair, n (%)                  |                   |                   | 0.46    |
| Data available                         | 258 (87)          | 86 (77)           |         |
| Without TAP                            | 143 (55)          | 46 (52)           |         |
| TAP                                    | 62 (24)           | 17 (22)           |         |
| TAP and pulmonary artery plasty        | 53 (21)           | 23 (26)           |         |
| Time from repair (years)               | 14 (6-48)         | 14 (4-44)         | 0.53    |
| Follow-up (years)                      | 10.1 (0.1-12.9)   | n/a               | -       |
| PVR during follow-up, n (%)            | 119/292 (41)      | n/a               | -       |
| **Clinical status and history**        |                   |                   |         |
| Initial palliation, n (%)              | 67/282 (24)       | 26/101 (26)       | 0.69    |
| Previous PVR, n (%)                    | 70/296 (24)       | 24/111 (22)       | 0.69    |
| NYHA>class I, n (%)                    | 96/296 (32)       | 52/109 (48)       | 0.007   |
| 12-lead ECG: QRS duration (ms)         | 147 ± 22          | 141 ± 25          | 0.03    |
| **Cardiopulmonary exercise test**      |                   |                   |         |
| Peak VO$_2$ at VAT (ml/min/kg)         | 24.3 ± 8.5        | 23.8 ± 7.4        | 0.77    |
| Measure | Mean ± SD | Median (IQR) | p-value |
|---------|-----------|--------------|---------|
| Peak VO<sub>2</sub> (ml/min/kg) | 31.1 ± 8.4 | 31.2 ± 9.2 | 0.85 |
| Peak heart rate (/min) | 172 (79-204) | 171 (50-200) | 0.42 |

**Echocardiography**

| Measure | Mean ± SD | Median (IQR) | p-value |
|---------|-----------|--------------|---------|
| Peak RVOT gradient (mmHg) | 16.0 (1.4-83.0) | 17.3 (2.2-76.2) | 0.27 |
| Tricuspid valve regurgitation > moderate, n (%) | 22/211 (10) | 4/50 (8) | 0.79 |

**CMR study**

| Measure | Mean ± SD | Median (IQR) | p-value |
|---------|-----------|--------------|---------|
| RVEDVi (ml/m<sup>2</sup>) | 116 (67-242) | 113 (54-247) | 0.12 |
| RVESVi (ml/m<sup>2</sup>) | 57 (20-186) | 57 (22-127) | 0.62 |
| RVSVI (ml/m<sup>2</sup>) | 60 ± 16 | 56 ± 18 | 0.01 |
| RVEF (%) | 51 ± 9 | 49 ± 10 | 0.21 |
| PR (%) | 27 (0-65) | 27 (0-85) | 0.87 |
| RV mass to volume ratio | 0.29 (0.08-0.74) | 0.28 (0.11-0.63) | 0.36 |

| Measure | Mean ± SD | Median (IQR) | p-value |
|---------|-----------|--------------|---------|
| LVEDVi (ml/m<sup>2</sup>) | 82 (43-195) | 76 (35-126) | 0.001 |
| LVESVi (ml/m<sup>2</sup>) | 34 (17-166) | 32 (15-60) | 0.22 |
| LVSVI (ml/m<sup>2</sup>) | 47 (23-87) | 43 (21-82) | 0.007 |
| LVEF (%) | 58 (15-74) | 57 (9-71) | 0.42 |
| LV mass (g/m<sup>2</sup>) | 54 (30-127) | 55 (22-87) | 0.65 |
| LV mass to volume ratio | 0.69 ± 0.18 | 0.76 ± 0.24 | 0.10 |

**Feature tracking analysis**

| Measure | Mean ± SD | Median (IQR) | p-value |
|---------|-----------|--------------|---------|
| RV-LS (%) | -12.9 ± 4.6 | n/a | - |
| RV-CS (%) | -15.2 ± 4.1 | n/a | - |
| LV-LS (%) | -13.8 ± 5.0 | n/a | - |
| LV-CS (%) | -20.7 ± 4.8 | n/a | - |
|                  | Value                  | n/a   | -  |
|------------------|------------------------|-------|----|
| LV-RS (%)        | 25.3 ± 8.8             | n/a   | -  |
| RV EDSR LS (1/s) | 0.67 (0.22-3.76)       | n/a   | -  |
| RV EDSR CS (1/s) | 0.93 (0.29-2.71)       | n/a   | -  |
| LV EDSR LS (1/s) | 1.08 (0.25-4.03)       | n/a   | -  |
| LV EDSR CS (1/s) | 1.49 (0.41-2.76)       | n/a   | -  |
| Interventricular Dysynchrony LS (ms) | 44 (0-607) | n/a | - |
| Interventricular Dysynchrony CS (ms) | 46 (0-159) | n/a | - |

CMR, cardiovascular magnetic resonance; TOF, tetralogy of Fallot; PA, pulmonary atresia; TAP, transannular patch; n/a, not applicable; PVR, pulmonary valve replacement; NYHA, New York Heart Association functional class; VO₂, oxygen uptake; VAT, ventilator anaerobic threshold; RVOT, right ventricular outflow tract; RV, right ventricle; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; PR, pulmonary regurgitation; LS, longitudinal strain; CS, circumferential strain; RS, radial strain; EDSR, early diastolic strain rate. Data are displayed as mean with 1 standard deviation or as median and range.
Table S2. Univariable Cox proportional-hazard analysis considering the composite endpoint of death and sustained ventricular tachycardia (VT) that occurred in 8 patients (11 patients with non-sustained VT considered as no event). Peak echocardiographic RVOT gradient remained a significant predictor for adverse events (HR 1.04, 95%-CI 1.00-1.07, p=0.046).

| Parameter                                      | HR      | 95% CI      | p-value |
|------------------------------------------------|---------|-------------|---------|
| Diagnosis (TOF/PA vs. TOF)                     | 2.48    | 0.29-20.9   | 0.41    |
| Age at CMR (years)                             | 1.08    | 1.02-1.13   | 0.004   |
| Age at corrective surgery (years)              | 1.12    | 1.03-1.23   | 0.01    |
| Type of repair (TAP vs. no TAP)                | 1.59    | 0.36-7.09   | 0.55    |
| Time from repair (years)                       | 1.08    | 1.01-1.17   | 0.03    |
| Initial palliation (yes/no)                    | 5.77    | 0.96-34.5   | 0.06    |
| Previous PVR (yes/no)                          | 3.35    | 0.84-13.4   | 0.09    |
| PVR during follow-up (yes/no)                  | 1.64    | 0.36-7.38   | 0.52    |
| NYHA class > I (yes/no)                        | 4.35    | 1.02-18.5   | 0.05    |
| QRS (ms)                                       | 0.32    | 0.98-1.05   | 0.32    |
| Peak VO2 at VAT (ml/min/kg)                    | 0.93    | 0.83-1.04   | 0.20    |
| Peak VO2 (ml/min/kg)                           | 0.89    | 0.81-0.96   | 0.004   |
| Peak heart rate (/min)                         | 0.97    | 0.95-0.99   | 0.002   |
| RVOT gradient (mmHg)                           | 1.04    | 1.00-1.07   | 0.046   |
| Tricuspid valve regurgitation > moderate (yes/no) | 0.96    | 0.11-8.30   | 0.96    |
| RVEDVi (ml/m²)                                 | 1.02    | 1.01-1.04   | 0.01    |
| RVESVi (ml/m²)                                 | 1.04    | 1.02-1.06   | <0.001  |
| RVSVI (ml/m²)                                  | 0.98    | 0.94-1.03   | 0.50    |
| RVEF (%)                                       | 0.91    | 0.86-0.97   | 0.004   |
| PR (%)                                         | 0.99    | 0.95-1.04   | 0.79    |
| RV mass (g/m²)                                 | 1.02    | 0.98-1.06   | 0.37    |
| RV mass to volume ratio                        | 0.72    | 0.01-341.3  | 0.92    |
| LVEDVi (ml/m²)                                 | 1.05    | 1.03-1.07   | <0.001  |
| LVESVi (ml/m²)                                 | 1.04    | 1.02-1.06   | <0.001  |
| LVSVI (ml/m²)                                  | 1.02    | 0.94-1.10   | 0.65    |
| LVEF (%)                                       | 0.92    | 0.87-0.96   | 0.001   |
| LV mass (g/m²)                                 | 1.03    | 1.00-1.07   | 0.05    |
| LV mass to volume ratio                        | 0.54    | 0.01-42.3   | 0.78    |
| RV-LS (%)                                      | 1.25    | 1.03-1.52   | 0.02    |
| RV-CS (%)                                      | 1.15    | 1.18-1.89   | 0.001   |
| LV-LS (%)                                      | 1.18    | 1.00-1.39   | 0.05    |
| LV-CS (%)                                      | 1.32    | 1.15-1.52   | <0.001  |
| LV-RS (%)                                      | 0.81    | 0.71-0.91   | 0.001   |
| RV EDSR LS (1/s)                               | 1.30    | 0.24-7.13   | 0.77    |
| RV EDSR CS (1/s)                               | 0.01    | 0.01-0.50   | 0.02    |
| LV EDSR LS (1/s)                               | 0.17    | 0.02-1.42   | 0.10    |
| LV EDSR CS (1/s)                               | 0.01    | 0.01-0.19   | 0.002   |
|                         |      |         |       |
|-------------------------|------|---------|-------|
| Interventricular Dysynchrony LS (ms) | 1.01 | 1.00-1.01 | 0.03  |
| Interventricular Dysynchrony CS (ms)  | 1.00 | 0.99-1.01 | 0.61  |

CMR, cardiovascular magnetic resonance; TOF, tetralogy of Fallot; PA, pulmonary atresia; TAP, transannular patch; PVR, pulmonary valve replacement; NYHA, New York Heart Association functional class; VO₂, oxygen uptake; VAT, ventilator anaerobic threshold; RVOT, right ventricular outflow tract; RV, right ventricle; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction; PR, pulmonary regurgitation; LS, longitudinal strain; CS, circumferential strain; RS, radial strain; EDSR, early diastolic strain rate.
**Table S3.** Differences in freedom from pulmonary valve replacement in the different subgroups according to the peak RVOT gradient (< 15, 15-30 and > 30 mmHg) and the severity of pulmonary regurgitation (PR < 25% and PR ≥ 25%). Statistical comparisons were made using the Log Rank (Mantel-Cox) test.

| Subgroup                  | PR < 25%, < 15 mmHg | PR ≥ 25%, < 15 mmHg | PR ≥ 25%, 15-30 mmHg | PR ≥ 25%, >30 mmHg | PR < 25%, 15-30 mmHg | PR < 25%, >30 mmHg |
|---------------------------|---------------------|---------------------|----------------------|-------------------|----------------------|-------------------|
| PR < 25%, < 15 mmHg       | -                   | <0.001              | <0.001               | <0.001            | 0.66                 | <0.001            |
| PR ≥ 25%, < 15 mmHg       | <0.001              | -                   | 0.37                 | 0.71              | <0.001               | 0.95              |
| PR ≥ 25%, 15-30 mmHg      | <0.001              | 0.37                | -                    | 0.31              | 0.001                | 0.48              |
| PR ≥ 25%, >30 mmHg        | <0.001              | 0.71                | 0.31                 | -                 | <0.001               | 0.68              |
| PR < 25%, 15-30 mmHg      | 0.66                | <0.001              | 0.001                | <0.001            | -                    | <0.001            |
| PR < 25%, >30 mmHg        | <0.001              | 0.95                | 0.48                 | 0.68              | <0.001               | -                 |
Figure S1. Graph displaying freedom from composite endpoint using Kaplan-Meier curves (graph bars indicating the 95% confidence intervals). The study population was divided into different subgroups according to the peak right ventricular outflow tract (RVOT) gradient (< 25 mmHg and ≥ 25 mmHg) and the severity of pulmonary regurgitation (PR < 25% and PR ≥ 25%). Statistical comparisons between the subgroups were assessed using the Log Rank (Mantel-Cox) test (p-values are displayed in the corresponding table).

Patients with moderate PR and a peak RVOT gradient ≥ 25 mmHg demonstrated significantly more adverse events than patients with moderate PR and a peak RVOT gradient < 25 mmHg (p<0.001). In patients with severe PR ≥ 25% RVOT gradients above or below 25 mmHg led to no significant difference (p=0.38).
VT, ventricular tachycardia; CMR, Cardiovascular Magnetic Resonance; RVOT, right ventricular outflow tract; HR, hazard ratio; CI, confidence interval