Is right ventricular resynchronization the key to both right and left ventricular remodeling?

Franziska Markel, MD, PhD, Christian Paech, MD, PhD, Roman Antonin Gebauer, MD, PhD, FHRS

From the Department for Pediatric Cardiology, University of Leipzig - Heart Center, Leipzig, Germany.

Introduction

Many patients with corrected tetralogy of Fallot (TOF) suffer from right ventricular (RV) dysfunction during long-term follow-up. Besides a chronic pressure or volume overload caused by pulmonary regurgitation or stenosis, electromechanical dyssynchrony due to right bundle branch block (RBBB), may represent an incompletely understood cause for RV dysfunction. Hui and colleagues¹ noted a dyssynchrony in 93% of pediatric patients after repair of the TOF. In these patients a pulmonary valve replacement may not be sufficient for cardiac remodeling. To date there are few data on RV cardiac resynchronization therapy (CRT) in patients with diminished RV function. Janousek and colleagues² showed a positive impact of the atrial synchronized RV free wall pacing regarding the QRS width and RV function. Resynchronization was achieved by optimal fusion of the pacing-induced depolarization wave with the spontaneous ventricular activation via the atroventricular node and native cardiac conduction system, resulting in the narrowest QRS complex and elevation of the blood pressure. They could demonstrate that CRT decreases the contraction delay between RV septum and free wall and leads to a better contraction efficiency and systolic output.² To date there are no data concerning the impact of improved RV function on the left ventricular (LV) function/remodeling.

Case report

A 32-year-old male patient with repaired TOF presented in our hospital for a regular follow-up with impairment of the RV function, resulting in a reduced physical capacity (NYHA class II). The patient underwent surgical correction (ventricular septal defect patch closure, pulmonary valvectomy, transannular patch, and subpulmonic infundibulectomy) at the age of 3 years and pulmonary valve replacement with a Hancock prosthesis, ablation of the cavo-tricuspid isthmus owing to atrial flutter, and implantation of an electric defibrillator owing to documented ventricular fibrillations (ventricular tachyarrhythmias) at the age of 18 years. The implantable cardioverter-defibrillator had been removed 10 years later after a successful ablation of monomorphic ventricular tachycardias. At the initial presentation at the age of 18 years the electrocardiogram (ECG) already showed a complete RBBB with a QRS width of 160 ms, which currently showed a duration of 200 ms. Echocardiography showed only mild regurgitation and no significant stenosis of the pulmonary xenograft. The cardiac magnetic resonance imaging showed a decreased RV ejection fraction (EF) of 30%, an enlarged right ventricle, and RV dyssynchrony, showing a slight progression compared to a previous magnetic resonance image. The LV EF was reduced to 40%.

In synopsis of the results, we opted for a RV CRT to improve the RV function. Two bipolar endocardial leads were placed in the RV via the left subclavian vein. One lead was placed at the RV free wall (site of the latest activation, QRS measured width 120 ms) and a second in the RV apex, and an atrial lead was placed in the right atrium (Figure 1). The atroventricular (AV) delay was set to achieve narrowing of the QRS width via fusion of the paced and intrinsic ventricular depolarization wave. Immediately

KEY TEACHING POINTS

- The causes of right ventricular (RV) dysfunction in patients with corrected tetralogy of Fallot can be diverse. Besides residual defects, electric dyssynchrony, owing to right bundle branch block, seems to represent an underestimated cause.
- RV resynchronization might represent a promising therapeutic option to remedy right bundle branch block and restore RV synchrony and function.
- It can be assumed that cardiac resynchronization therapy can lead to cardiac remodeling; experimental animal studies even show a positive impact on a cellular level.

KEYWORDS Cardiac remodeling; Cardiac resynchronization; Electrical dyssynchrony; Right bundle branch block; Right ventricular dysfunction; Tetralogy of Fallot

Address reprint requests and correspondence: Dr Franziska Markel, Department for Pediatric Cardiology, University of Leipzig - Heart Center, Strümpellstr. 39, 04289 Leipzig, Germany. E-mail address: Franziska.markel@helios-gesundheit.de.
following RV CRT, the QRS duration was markedly decreased (QRS preinterventionally 200 ms, postinterventionally QRS 120 ms; Figures 2 and 3) and the complete RBBB disappeared.

At 6 months follow-up, the LV function has markedly improved from LV EF 40% preinterventionally to LV EF 53% postinterventionally. The RV EF showed no measurable improvement, yet a slight reduction of RV end diastolic volume (387 mL postinterventionally compared to 410 mL pre-interventionally) could be seen. At 12 months follow-up a slight sonographic improvement of the RV function could be noted.

Discussion
There are only few data about RV resynchronization in patients with corrected TOF. Apart from residual defects like pulmonary valve regurgitation or stenosis, a RBBB may also lead to electromechanical dyssynchrony with enlarged RV volume and diminished RV EF.

Paech and colleagues\(^3\) claim that RV dyssynchrony after correction of TOF plays an underestimated role in RV remodeling after pulmonary valve replacement (percutaneous pulmonary valve implantation). The authors showed a correlation between the QRS width and the probability for RV remodeling after percutaneous pulmonary valve implantation, with only patients with a QRS width below 140 ms showing RV remodeling.\(^3\) As the ECG of our patient showed a QRS width over 180 ms, the possibility of a significant remodeling was reduced beforehand. Pathophysiologically, one can assume that at some point the myocardial fibers are overstretched and lose the ability to contract. Furthermore, Hoppe and colleagues\(^4\) state that the potential of an electrical dyssynchrony becoming a mechanical one is dependent on the genetic background of each patient. Therefore, it may be assumed that the remodeling is relying on the genetic component as well. In experimental animal studies, it could be demonstrated that an electrical dyssynchrony over time results in changes in gene expression leading to, for example,
altered metabolic pathways and matrix remodeling. CRT could reverse these changes on different levels, owing to heterogeneous expression in different regions of the left ventricular wall. There is also a good case to believe that the right ventricle responds to a different extent to the CRT on a cellular level. Additionally, remodeling is a long process; therefore, a rapid improvement cannot be anticipated in every patient. Nevertheless, postinterventionally we noted a slightly diminished RV volume, which may be interpreted as the beginning of the process of ventricular remodeling. Therefore, it seems reasonable to suggest a better LV preload as reason for the relevant increase in the LV function in our patient. There are several studies that demonstrate a positive effect of LV CRT on the RV function, indicating the dependence of both ventricles in biventricular circulation.

In short, the presented case emphasizes the need for further studies to evaluate the relevance of RV CRT in patients with RBBB after cardiac surgery and reduced RV function. In particular, prospective, multicentric studies are needed to evaluate long-term outcomes and define the indications and patient selection criteria for a long-term RV CRT.

Conclusion
CRT may be a promising treatment option for both right heart failure and reduced left heart function in patients after repaired TOF as a supplementary therapy to surgical or interventional resolution of residual defects. Further studies are needed to further enhance knowledge about this promising therapeutic option.

Acknowledgments
We acknowledge support from the German Research Foundation (DFG) and Universität Leipzig within the program of Open Access Publishing.

References
1. Hui W, Slorach C, Dragulescu A, Mertens L, Bijnen B, Friedberg MK. Mechanisms of right ventricular electromechanical dyssynchrony and mechanical inefficiency in children after repair of tetralogy of Fallot. Circ Cardiovasc Imaging 2014; 7:610–618.
2. Janoušek J, Kovanda J, Ložek M, et al. Pulmonary right ventricular resynchronization in congenital heart disease. Acute improvement in right ventricular mechanics and contraction efficiency. Circ Cardiovasc Imaging 2017;10.
3. Paech C, Dähnert I, Riede FT, et al. (2017). QRS width as a predictor of right ventricular remodeling after percutaneous pulmonary valve implantation. Pediatr Cardiol 2017;38:1277–1281.
4. Hoppe L, Wagner F, Weidenbach M, et al. Influence of ventricular ectopic beats on the systemic ventricular function in patients with congenital heart disease. A long-term longitudinal study. Ann Pediatr Cardiol. In press.
5. Barth AS, Aiba T, Halperin V, et al. (2009). Cardiac resynchronization therapy corrects dyssynchrony induced regional gene expression changes on a genomic level. Circ Cardiovasc Genet 2009;2:371–378.
6. Sharma A, Lavie CJ, Vallakati A, et al. Changes in parameters of right ventricular function with cardiac resynchronization therapy. Clin Cardiol 2017;40:1033–1043.