ARTICLE IN PRESS
IJCA-26278; No of Pages 5
International Journal of Cardiology xxx (2018) xxx–xxx
Contents lists available at ScienceDirect
International Journal of Cardiology
journal homepage: www.elsevier.com/locate/ijcard

Biventricular dyssynchrony on cardiac magnetic resonance imaging and its correlation with myocardial deformation, ventricular function and objective exercise capacity in patients with repaired tetralogy of Fallot☆

Pantelis Kalaitzidis [a], Stefan Orwat [a], Aleksander Kempny [e], Radke Robert [a], Brigitte Peters [d], Samir Sarikouch [b], Philipp Beerbaum [c], Helmut Baumgartner [a], Gerhard-Paul Diller [a,*], for the Competence Network for Congenital Heart Defects, DZHK (German Center for Cardiovascular Research)

[a] Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital Muenster, Muenster, Germany
[b] Department of Heart-, Thoracic-, Transplantation- and Vascular Surgery, Hannover Medical School, Germany
[c] Department of Pediatric Cardiology and Pediatric Intensive Care, Hannover Medical School, Germany
[d] Institute for Biometry and Medical Informatics, University of Magdeburg, Germany
[e] Adult Congenital Heart Centre and Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, UK

ARTICLE INFO

Article history:
Received 9 October 2017
Received in revised form 9 March 2018
Accepted 2 April 2018
Available online xxxx

Keywords:
Tetralogy of Fallot
Magnetic resonance imaging
Dyssynchrony

ABSTRACT

Background: Electrical dyssynchrony and prolonged QRS duration are common in patients with repaired tetralogy of Fallot (ToF). It has been linked to increased risk of sudden cardiac death and right ventricular (RV) dysfunction. We investigated myocardial dyssynchrony using cardiac magnetic resonance imaging (CMR) and feature tracking analysis (FT) in this setting and compared it to myocardial deformation, conventional parameters of ventricular dysfunction and clinical parameters.
Methods and results: Patients underwent standardized CMR investigations as part of a nationwide study. We prospectively assessed myocardial deformation and analysed regional wall motion abnormalities of the RV and the left ventricle (LV) using CMR-FT. The main measure of dyssynchrony was the maximal time difference (wall motion delay) of the regional strain as a parameter of mechanical biventricular dyssynchrony. In addition, clinical parameters and measures of cardiopulmonary exercise capacity were available. Overall 345 patients were included. Parameters of biventricular wall motion delay correlated significantly with global FT-strain parameters ($p < 0.0001$ for all imaging planes assessed). Furthermore, we found a significant correlation between circumferential RV motion delay and QRS duration ($p = 0.006$). Higher LV and RV wall motion delay parameters were also associated with lower peak oxygen consumption ($p < 0.05$) and a worse LV and RV ejection fraction ($p < 0.02$).
Conclusions: Assessment of mechanical dyssynchrony is feasible using CMR-FT in ToF patients. Parameters of mechanical dyssynchrony correlate with electrical dyssynchrony, biventricular function and objective exercise capacity in this setting. Due to the weak degree of correlation, however, the clinical significance of these findings remains to be clarified by further studies.

1. Introduction

Contemporary patients with tetralogy of Fallot (ToF) are commonly affected by pulmonary valve regurgitation, right ventricular (RV) enlargement, biventricular dysfunction and an increased risk for malignant arrhythmias and sudden cardiac death [1–4]. Identification of ToF patients at particularly high risk of malignant arrhythmias and sudden cardiac death remains a major focus of research and novel parameters correlating with risk of adverse events are required. So far, parameters such as prolonged QRS duration ≥180 ms, pulmonary regurgitation, reduced right and especially left ventricular function, the presence of inducible ventricular tachycardia, impaired exercise capacity and potentially extensive RV scarring on late gadolinium cardiac magnetic

Abbreviations: Circ, circumferential; CMR, cardiac magnetic resonance imaging; CS, circumferential strain; EF, ejection fraction; FT, feature tracking; LAX, long axis; Long, longitudinal; LS, longitudinal strain; LV, left ventricle; rad, radial; RS, radial strain; RV, right ventricle; SAX, short axis; SCD, sudden cardiac death; VO_2, oxygen uptake.

☆ This study was supported by a research grant from the EMAH Stiftung Karla Voellm, Krefeld, Germany and by the German Competence Network for Congenital Heart Defects (funded by the German Federal Ministry of Education and Research, BMBF - FKZ 01G10210, 01GI0601).

* Corresponding author at: Division of Adult Congenital and Valvular Heart Disease, Department of Cardiovascular Medicine, University Hospital of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany.
E-mail address: gerhard.diller@ukmuenster.de (G.-P. Diller).

https://doi.org/10.1016/j.ijcard.2018.04.005
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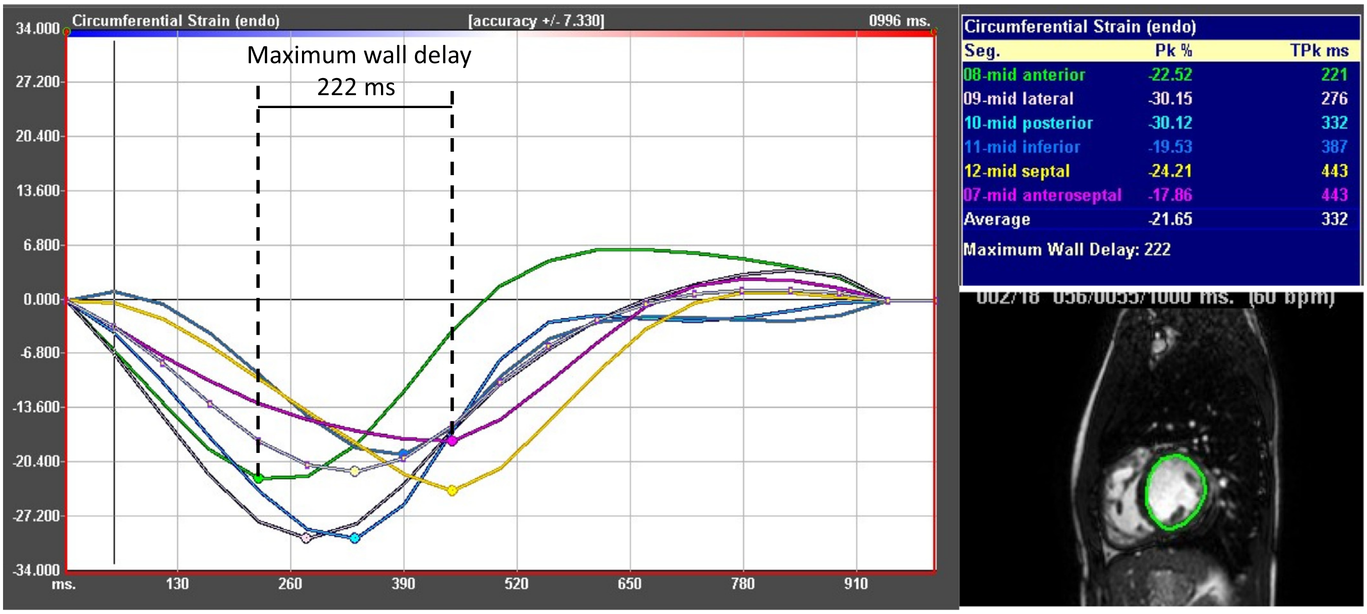

Fig. 1. Illustration of the measurement of maximum wall motion delay on feature tracking cardiac magnetic resonance imaging.

resonance imaging (CMR) have been related to outcome in this cohort [5–8]. Beyond non-invasive imaging, elevated left ventricular end-diastolic pressures on cardiac catheterization have also been identified as a major prognostic marker in this setting [8]. While the utility of regular transthoracic echocardiography in predicting outcome has been established [9], CMR has emerged as the gold standard imaging modality for assessing ventricular volumes in ToF patients. It has only recently, however, become possible to quantify mechanical dyssynchrony on CMR using standard CMR cine images. This is due to the introduction of CMR feature tracking (FT) analysis - a technique for the quantification of myocardial strain using standard steady-state-free precession (SSFP) images [10]. We have reported on the feasibility of using FT analysis for measuring myocardial deformation and its potential prognostic value [11,12]. However, information on the potential clinical utility of FT derived parameters of mechanical dyssynchrony are limited in contemporary ToF patients [13,14]. The pathophysiologic rationale for the evaluation of measures of mechanical dyssynchrony is provided by the observation that electrical dyssynchrony is a prognostic marker in ToF patients and by previous studies suggesting an association between mechanical asynchrony and outcome [6,14,21,30].

The current study was designed to evaluate the potential association between biventricular mechanical dyssynchrony on FT-CMR with parameters of biventricular mechanics, exercise capacity, clinical data and outcome in a large multicenter cohort of ToF patients.

2. Materials and methods

The current study included patients enrolled in a nationwide, prospective study of ToF patients run by the German Competence Network for Congenital Heart Defects as described before [15]. In essence, patients with repaired ToF older than 8 years were recruited at various German centers (24 centers overall) between 2005 and 2008. All patients without contraindications for CMR (such as implanted pacemakers or ICD devices) were invited to participate. All enrolled ToF-patients underwent CMR investigations (avoiding sedation) using a standardized CMR protocol. Acquired datasets were stored on a central archiving database in a pseudonymized format. Further details on the CMR protocol, quality assurance measures and conventional (volumetric) analysis have been reported [15–17].

Feature tracking analysis was performed prospectively on **all** digitally archived datasets by using the TomTec 2D CPA MR software (TomTec, Unterschleissheim, Germany, Version 1.1.2.36-B) by GD and SO. There was no difference image quality between the right and left ventricle. Analysis was performed separately for both ventricles by delineating the endocardial border followed by automatic FT computation. For all analysis the quality and adequacy of myocardial displacement and the tracking contour was controlled visually and the analysis repeated if required. Longitudinal and radial deformation parameters of the LV and RV were assessed in a four chamber view. Circumferential parameters of both LV and RV were assessed in the short axis view at the level of the papillary muscles. Additional details of the FT algorithm have been published by us and others [18–21]. Data on reproducibility of the FT-method in the setting of ToF has also been provided by our group [22].

As described previously [12], available clinical characteristics included the NYHA (New York Heart Association) functional class, the QRS duration on standard 12-lead ECG, as well as details of previous interventional and surgical procedures. Patients also were subjected to symptom-limited cardiopulmonary exercise testing on a treadmill or bicycle ergometer at the time of CMR [23].

Mechanical dyssynchrony was assessed by quantifying the maximum wall delay of the longitudinal, radial (both in a long axis and short axis view) as well as circular contraction of the right and left ventricle. The method of assessment of maximum wall delay is illustrated in Fig. 1.

Follow-up was secured by using competence network infrastructure and/or by contacting local institutions or residents' registration office if required. As an endpoint of the study we chose a composite of documented ventricular tachycardia (sustained or non-sustained) or cardiac death, which included aborted cardiac death. The study protocol has been approved by the relevant ethics committee and all patients/guardians gave informed consent before recruitment/inclusion in the study.

2.1. Statistics

Depending on data distribution parameter values are given as mean and standard deviation or median and interquartile range (25th and 75th percentile). Categorical variables are shown as frequencies and percentages. The association between parameters of mechanical dyssynchrony, myocardial deformation parameters, conventional volumetric markers of ventricular function and clinical status was assessed by Spearman's rank regression analysis. In addition, the potential association with outcome was studied by Cox proportional-hazard analysis. Due to the limited number of events no multivariate analyses were performed. For all analyses, a 2-tailed p-value <0.05 was used as the criterion for statistical significance. Statistical analyses were performed using MedCalc 17.6 (MedCalc Software, Mariakerke, Belgium) and R version 3.3.0 (The R Foundation for Statistical Computing).

3. Results

Overall, adequate CMR images for FT assessment of mechanical dyssynchrony were available in 345 patients (56% male, mean age 17.5 ± 8.3 years, RV end-diastolic volume index 121 ± 33 ml/m^2, RV ejection fraction $50 \pm 9\%$; LV ejection fraction $57 \pm 9\%$). Values of the measures of mechanical dyssynchrony are provided in Table A (Online Appendix). The majority of patients were asymptomatic and the objective exercise capacity as assessed by cardiopulmonary exercise testing

Please cite this article as: P. Kalaitzidis, et al., Biventricular dyssynchrony on cardiac magnetic resonance imaging and its correlation with myocardial deformation, ventricular func..., Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.04.005