ARTICLE IN PRESS
IJCA-26849; No of Pages 6
International Journal of Cardiology xxx (2018) xxx–xxx
Contents lists available at ScienceDirect
International Journal of Cardiology
journal homepage: www.elsevier.com/locate/ijcard

The impact of multipole pacing on left ventricular function in patients with cardiac resynchronization therapy — A real-time three-dimensional echocardiography approach

Severin Weigand [a,*,1], Michael Karl [a,1], Amir Brkić [a,1], Carsten Lennerz [a,b,1], Christian Grebmer [a,1], Patrick Blažek [a,1], Marielouise Kornmayer [a,1], Claudia Schaarschmidt [a,1], Lorraine Wesemann [a,1], Tilko Reents [a,1], Gabriele Hessling [a,1], Isabel Deisenhofer [a,1], Christof Kolb [a,1]

[a] *Deutsches Herzzentrum München, Klinik für Herz- und Kreislauferkrankungen, Abteilung für Elektrophysiologie, Faculty of Medicine, Technische Universität München, Munich, Germany*
[b] *DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany*

ARTICLE INFO

Article history:
Received 11 March 2018
Received in revised form 22 July 2018
Accepted 9 August 2018
Available online xxxx

Keywords:
Cardiac resynchronization therapy
Heart failure
Left ventricular ejection fraction
Multipole pacing
Optimization
Systolic dyssynchrony index

ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is standard of care in heart failure (HF), however this technique is associated with a non-responder rate of 30%. Multipole pacing (MPP) with a quadripolar lead may optimize CRT and responder rate by creating two electrical wave fronts in the left ventricular (LV) myocardium simultaneously in order to reduce mechanical dyssynchrony. The objective of this study was to investigate the acute impact of MPP on LV function by assessing systolic dyssynchrony index (SDI) and left ventricular ejection fraction (LVEF) via real-time three-dimensional echocardiography (RT3DE).
Methods: In 41 consecutive patients (87.8% male; mean age 66.0 ± 12.7 years) who received CRT defibrillators with a quadripolar LV lead, RT3DE datasets were acquired the day after implantation under the following pacing configurations: Baseline AAI, conventional biventricular pacing using distal or proximal LV poles and MPP. Datasets were analyzed in paired samples evaluating SDI and LVEF depending on programmed pacing modality.
Results: MPP resulted in statistically significant reduction of SDI compared to baseline (6.3%; IQR 4.4–7.8 and 9.9%; IQR 8.0–12.7; $p < 0.001$) and to conventional biventricular pacing using distal (7.6%; IQR 6.5–9.1; $p < 0.001$) or proximal (7.4%; IQR 6.2–8.8; $p < 0.001$) LV poles respectively. MPP yielded significant increase in LVEF compared to baseline (30.6%; IQR 25.8–37.5 and 27.2%; IQR 21.1–33.6; $p < 0.001$) and to conventional biventricular pacing configuration with distal (28.1%; IQR 22.1–34.5; $p < 0.001$) or proximal (28.6%; IQR 23.2–34.9; $p < 0.001$) LV poles respectively.
Conclusions: Multipole pacing improves mechanical dyssynchrony of the left ventricular myocardium as assessed by SDI and LVEF.

1. Introduction

Cardiac resynchronization therapy (CRT) with biventricular pacing is standard of care in the treatment of heart failure (HF). According to current guidelines implantation of a CRT system is recommended for patients with left ventricular ejection fraction (LVEF) ≤ 35%, a wide QRS complex (either left bundle branch block ≥ 130 ms or non-left bundle branch block ≥ 150 ms) and heart failure symptoms under optimal medical therapy [1]. Despite of adequate patient selection up to one-third of CRT recipients are considered non-responders [2–6].

Recently, quadripolar LV leads have been introduced. Attached to the corresponding cardiac implantable electronic device, pacing impulses can be delivered safely and efficiently to different areas of the LV at the same time — the so called multipole pacing (MPP) [7,8]. Creating two concurrent electrical wave fronts in the left ventricular myocardium may optimize CRT response by improving LV wall movement synchrony and reversing the LV-remodeling due to ischemic scars or non-ischemic cardiomyopathy [9]. Compared to conventional biventricular pacing, stimulation of the LV from two sites has been shown to provide an acute increase in systolic function and contractility [10–13]. Furthermore, Pappone et al. have demonstrated a greater LV reverse remodeling and increased LV function as well as a reduced New York Heart Association (NYHA) functional class at 12 months after activation of MPP [14].

The assessment of CRT response with activated MPP is limited to data derived from hemodynamic measurements and standard two-dimensional echocardiography (2DE) so far. However, these methods

* Corresponding author at: Deutsches Herzzentrum München, Lazarettstrasse 36, 80636 München, Germany.
E-mail address: weigand@dhm.mhn.de (S. Weigand).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2018.08.033
0167-5273/© 2018 Published by Elsevier B.V.

have a low predictive value to examine long-term response, as described in the PROSPECT trial [15]. Quantifying the systolic dyssynchrony index (SDI) by real-time three-dimensional echocardiography (RT3DE) is well established and considered superior in the prediction of response [16,17]. A meta-analysis of Kleijn et al. established a weighted mean of 9.8% as the relevant cut-off value for SDI with a sensitivity and specificity of 93% and 75%, respectively [18]. However, it is unclear how the SDI is influenced by multipole pacing. Therefore, the primary aim of the study was to investigate the impact of MPP on LV dyssynchrony by assessing SDI via RT3DE.

2. Methods

2.1. Study design and patient population

The presented MPP-trial is a prospective, single-centre study, conducted at German Heart Centre Munich, Technische Universität München, Munich, Germany. Patients with indication for cardiac resynchronisation therapy and sudden cardiac death prevention according to current guidelines were consecutively enrolled [1]. The inclusion criteria were medically refractory heart failure with NYHA class II to IV, LV dysfunction with LVEF ≤ 35% and a prolonged QRS complex with left bundle branch block (LBBB) ≥ 130 ms or non-left bundle branch block (Non-LBBB) ≥ 150 ms, respectively. Additionally, patients with frequent right-ventricular pacing and reduced LVEF were eligible for the study. Exclusion criteria were (1) previous cardiac surgery, (2) previous acute myocardial infarction, (3) coronary intervention within the last four weeks before study enrolment, (4) atrial fibrillation with insufficient rate control, (5) patients with suboptimal echocardiographic image quality, (6) pregnancy, (7) age < 18 years and (8) patients under tutelage or unwillingness to participate in the trial.

Eligible patients were supplied with an ICD-CRT device (Intica 7 HF-T QP, Biotronik, Berlin, Germany) ready to perform MPP, which was connected to standard right atrial (RA) and right ventricular (RV) leads as well as to a quadripolar LV lead designed for MPP (Sentus OTW QP L-85, Biotronik, Berlin, Germany). Potential benefits of such a quadripolar lead are an increased probability of avoiding phrenic nerve stimulation and achieving good pacing thresholds despite of close proximity between the lead and the phrenic nerve or ischemic scars respectively [19]. CRT implantation was performed following standard procedure and targeting LV lead position in a non-apical lateral position. Before discharge, SDI and LVEF were assessed in each patient in four different pacing configurations (see 1–4) following a standardized echocardiography protocol.

1) For baseline measurement, atrial pacing (AAI) with 80 bpm was programmed. In patients depending on permanent ventricular pacing the DDD mode with RV pacing at 80 bpm was used instead.
2) DDD mode with biventricular pacing from the two distal LV poles (LV1/2) was programmed, representing conventional CRT stimulation.
3) DDD mode with biventricular pacing from the proximal poles of the LV lead (LV3/4) was programmed, assessing the effect of stimulation far from the tip using a quadripolar lead in comparison to the traditional bipolar LV leads.
4) Finally, DDD mode with multipole pacing (MPP) was programmed. MPP was defined as simultaneous pacing from the two distal and the two proximal LV poles (LV1/2 + LV3/4).

During all measurements within the DDD mode, CRT devices were configured to a fixed atrioventricular (AV) delay of 120 ms and an interventricular (VV) delay of 0 ms. Within the MPP mode, a fixed intraventricular delay between LV1/2 and LV3/4 was set to 5 ms, the minimum value available.

2.2. Real-time three-dimensional echocardiography

The real-time three-dimensional echocardiography (RT3DE) was performed by an experienced operator the day after ICD-CRT implantation using Philips iE33 (Philips Healthcare, Andover, MA, USA) equipped with a ×3–1 matrix transducer. The operator was blinded to the pacing modality and in every patient all different pacing modes were chosen in a random order with a washout time of 10 min between measurements. Acquisition was performed with patients lying in left lateral position and intermittently holding breath to minimize artefacts. Subsequently, apical three-dimensional (3D) full-volume loops of the entire LV were generated over the period of five to six cardiac cycles adjusting angle and depth in order to reach an optimal temporal resolution.

The recorded datasets were processed offline and analyzed by two independent, blinded investigators using commercially available software (4D LV-Analysis 3.1, TomTec Imaging Systems, Munich, Germany). This software provides semi-automated detection of the endocardial border and creates a dynamic 3D model of the LV cavity during the cardiac cycle through automated sequential tracking, as described earlier [20,21]. If needed, the investigators corrected the endocardial contours, e.g. in order to differentiate between wall building endocardium and papillary muscle belonging to one of the mitral valve cusps. In the final analysis left ventricular ejection fraction (LVEF) was quantified and the systolic dyssynchrony index (SDI) was calculated as the standard deviation of the time to minimal systolic volume (TmSv) in a 16 segment model of the LV. Measurements were corrected for the RR interval and expressed as a percentage, in which lower SDI means reduced level of LV dyssynchrony [22–24] (Fig. 1).

Final programming of the CRT devices was left to the discretion of the treating physician.

2.3. Statistical analysis and sample size calculation

Categorical data is described by absolute and relative frequencies and compared using contingency tables. Quantitative data distributions were tested for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. Quantitative data was described as mean and standard deviation as well as minimum, maximum and IQR and compared using Mann-Whitney *U* test or student's *t*-test where appropriate. Comparisons of two dependent samples, such as repeated measurements with different pacing modes were done by Wilcoxon's matched pairs test if non-parametric analysis was necessary and matched pairs *t*-test if not. Correlation analyses of two metric variables were also performed according to the respective distribution, Spearman rank correlation analysis was used in case of significant deviations from normal distribution in at least one parameter, otherwise Pearson's correlation analysis was done. To investigate and assess the agreement of each two measurements, in particular within the reliability analyses for two raters (inter-rater reliability) and for the measures of one rater (intra-rater reliability), Bland-Altman's analysis was performed.

All statistical tests were performed two-sided with a significance level of 5%. An alpha adjustment for multiple testing was not applied, and the results were interpreted accordingly. Statistical calculations were done with SPSS Statistics 25 (SPSS Inc., IBM Company, Chicago, IL, USA).

At the time of study initiation, there was no data on differences of SDI between conventional biventricular pacing and MPP for patients with cardiac resynchronization therapy. The aim of the study was to investigate the acute change of SDI and LVEF after implantation of a CRT system comparing baseline atrial pacing, conventional biventricular pacing and multipole pacing. For a clinical significant increase in CRT response, we assumed a reduction of SDI by 30% with MPP in comparison to standard biventricular pacing (LV1/2) as used in many CRT-optimization trials [23,24]. Based on non-normally distributed SDI-levels, a power of 80%, a level of significance of 5% and a drop-out rate of 20% 40 patients had to be included.

2.4. Endpoints

Primary endpoint of the study was to determine the effect of multipole pacing on LV dyssynchrony as assessed by SDI in RT3DE. Predefined secondary endpoint was the effect of multipole pacing on the LVEF.

2.5. Ethics statement

Written informed consent was obtained from all patients before participation. The study complies with the principles of the Declaration of Helsinki and was approved by the institutional ethics committee as well as registered with clinicaltrials.gov under NCT03187470.

3. Results

3.1. Baseline characteristics

A total of 52 patients met the inclusion criteria. Analysis was performed on a total of 41 patients. Drop outs related to the RT3DE measurements were due to the implantation failure of a quadripolar lead ($N = 2$) or to micro dislodgement of the LV lead with loss of MPP functionality ($N = 9$). However, none of the patients required early lead revision.

Patients, who completed echocardiographic assessment of LV function, were 66.0 ± 12.7 years old and predominantly male (36 out of 41; 87.8%). Additional baseline characteristics of the study population are summarized in Table 1. The underlying cardiac disease was ischemic cardiomyopathy in 63.4% (26 out of 41) of the patients. Baseline QRS morphology was left bundle branch block in 78.0% (32 out of 41). Mean QRS width was 169.6 ± 28.6 ms, and 56.1% (23 out of 41) have never had a pacemaker/ICD implanted before (de novo ICD-CRT implantation).

3.2. Systolic dyssynchrony index (SDI)

Baseline pacing in AAI mode for patients with sufficient atrio-ventricular conduction or in DDD mode for patients without sufficient atrio-ventricular conduction resulted in a median SDI of 9.9% with an interquartile range (IQR) from 8.0 to 12.7 (Fig. 2A). The conventional

Please cite this article as: S. Weigand, et al., The impact of multipole pacing on left ventricular function in patients with cardiac resynchronization therapy — A real-time three-dimensional..., Int J Cardiol (2018), https://doi.org/10.1016/j.ijcard.2018.08.033