International Journal of Cardiology 168 (2013) 723–728

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Early pacing-induced systolic dyssynchrony is a strong predictor of left ventricular adverse remodeling: Analysis from the Pacing to Avoid Cardiac Enlargement (PACE) trial

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ARTICLE INFO

Article history:
Received 26 April 2012
Received in revised form 27 June 2012
Accepted 14 August 2012
Available online 1 September 2012

Keywords:
Pacing
Dyssynchrony
Left ventricular remodeling

ABSTRACT

Background: Right ventricular apical (RVA) pacing is associated with adverse left ventricular (LV) remodeling and biventricular (BiV) pacing may prevent it although the mechanisms remain unclear. The current study aimed to assess the role of early pacing-induced systolic dyssynchrony (DYS) to predict adverse LV remodeling.
Methods: Patients with standard pacing indications and normal LV ejection fraction were randomized either to BiV (n = 89) or RVA pacing (n = 88). Pacing-induced DYS, defined as the standard deviation of the time to peak systolic velocity (Dyssynchrony Index) > 33 ms in a 12-segmental model of LV, was measured by tissue Doppler echocardiography at 1 month.
Results: At 1 month, 59 patients (33%) had DYS which was more prevalent in RVA than BiV pacing group (52% vs. 15%, $\chi^2 = 28.3$, $p < 0.001$), though Dyssynchrony Index was similar at baseline (30 ± 14 vs. 26 ± 11 ms, $p = 0.06$). At 12 months, those developing DYS had significantly lower LV ejection fraction (55.1 ± 9.7 vs. 62.2 ± 7.9%, $p < 0.001$) and larger LV end-systolic volume (35.3 ± 14.3 vs. 27.0 ± 10.4 ml, $p < 0.001$) when compared to those without DYS. Reduction of ejection fraction ≥5% occurred in 67% (39 out of 58) of patients with DYS, but only in 18% (21 out of 115) in those without DYS ($\chi^2 = 40.8$, $p < 0.001$). Both DYS at 1 month (odds ratio [OR]: 4.725, $p = 0.001$) and RVA pacing (OR: 3.427, $p = 0.009$) were independent predictors for reduction of ejection fraction at 12 months.
Conclusion: Early pacing-induced DYS is a significant predictor of LV adverse remodeling and the observed benefit of BiV pacing may be related to the prevention of DYS.
Clinical trial registration: Centre for Clinical Trials number, CUHK_CCT00037 (URL: http://www.cct.cuhk.edu.hk/Registry/publictrialrecord.aspx?trialid=CUHK_CCT00037).

1. Introduction

Right ventricular apex (RVA) is the conventional site for ventricular lead placement in the pacing management of bradycardia by virtue of its easy accessibility and relative stability over time. However, the deleterious effect of RVA pacing on left ventricular (LV) systolic function and adverse clinical outcomes have been reported for patients with standard pacing indications [1–7], as well as patients who require cardioverter defibrillator therapy [8]. To date, the optimal pacing site for ventricular pacing remains unclear.

In patients with LV systolic dysfunction, the presence of LBBB pattern or prolonged QRS duration has been shown to be a surrogate marker for LV uncoordinated contraction as a result of electromechanical delay, or called systolic dyssynchrony (DYS) [9,10].The use of biventricular (BiV) pacing, or cardiac resynchronization therapy, leads to the improvement of clinical outcome and systolic function [11–15]. In patients with standard indications for bradycardia pacing and preserved systolic function, right ventricular apical pacing has been shown to induce DYS by various echocardiographic techniques [16–20]. In a retrospective study, RVA pacing induced mechanical dyssynchrony was associated with deterioration of LV systolic function [17,21]. Although other small studies showed that systolic dyssynchrony is the major pathophysiologic mechanism of reduction in LV function over time, such link has not been established in prospective clinical trials [16–18,22]. Furthermore, a recent study demonstrated that the propensity for the occurrence of DYS might be different between heart failure patients with LBBB and RVA pacing-induced LBBB in those with preserved LV systolic function [23].

Abbreviations: BiV, biventricular; DYS, systolic dyssynchrony; LV, left ventricle/left ventricular; LBBB, left bundle branch block; RVA, right ventricular apex.

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http://dx.doi.org/10.1016/j.ijcard.2012.08.005

BiV pacing has been suggested to preserve myocardial performance better than RVA pacing in the presence of atrioventricular block and normal systolic function in an animal model [24] and in acute hemodynamic studies in patients with LV ejection fraction >40% [25]. Recently the Pacing to Avoid Cardiac Enlargement (PACE) trial and the extended 2-year follow-up have consistently confirmed the superiority of BiV to RVA pacing in preventing the deterioration of ejection fraction and LV adverse remodeling in patients with bradycardia and preserved systolic function [26,27]. However, it is unclear whether this benefit is related to pacing-induced DYS. Therefore, we have undertaken a pre-specified analysis of the PACE trial to determine whether pacing-induced early systolic dyssynchrony is the major determinant of deterioration of ejection fraction and LV remodeling at 12 months. The results will provide important mechanistic insight into the association between RVA pacing induced DYS and subsequent LV adverse remodeling, and its possible prevention by BiV pacing.

2. Methods

2.1. Patients

The patient characteristics, study methods and results of the PACE trial have been published previously in detail [26,28]. In brief, this investigator-initiated clinical study was a prospective, double-blind, randomized, multicentre clinical trial to determine whether atrial-synchronized BiV pacing was superior to RVA pacing in preserving LV systolic function and avoiding adverse LV remodeling among patients with normal LV ejection fraction (≥45%) who had standard bradycardia pacing indications.

2.2. Study design

Patients enrolled into the study received an atrial-synchronized BiV pacemaker capable of delivering RVA and BiV pacing by appropriate device programming (InSync III, Medtronic Inc., Minneapolis, Minnesota, USA). In brief, the right atrial and right ventricular leads were positioned in the right atrial appendage and RVA respectively via a transvenous route. The LV lead was positioned preferentially to the posterolateral or lateral venous branches of coronary sinus (95% of patients). Two days after successful device implantation, patients were randomized to either RVA pacing (n = 88) or BiV pacing (n = 89) mode. Attending physicians were encouraged to maintain the same medications and doses for the study period, especially neurohormonal blockers and anti-arrhythmic drugs. Serial echocardiography and clinical assessments including the measurement of the distance covered on a 6-minute walk, and quality-of-life assessment with the use of the 36-Item Short-Form General Health Survey (SF-36) were performed at baseline, 1, 3, 6, 9 and 12 months. The study protocol was approved by local ethic committees of the institutions involved and complied with Declaration of Helsinki. Written informed consent was obtained from all patients (Centre for Clinical Trials, CUHK. Trial number: CUHK_CCT00037).

2.3. Echocardiography

Comprehensive and serial echocardiography was performed. For the assessment of LV volume and ejection fraction, real-time three-dimensional echocardiography was preferred and was performed (iE33, Phillips, Andover, MA, United States) in 90% of the patients, while biplane Simpson's method with 2-dimensional echocardiography was used in 10% of patients due to online availability. For three-dimensional echocardiography, pyramidal full volume images of LV with a matrix-array transducer (X3-1, 1.9/3.8 MHz) were acquired during breath holding to avoid artifacts. Images with clear LV endocardial border were stored digitally after adjusting the gain, compression as well as the sector width to ensure the frame rate >20 Hz. Quantitative analysis was performed with dedicated software (Q-Lab 7.0, Philips). An automatic border detection procedure was employed to measure the LV volumes and ejection fractions according to the preset mathematic model [29,30]. LV volumes and ejection fraction were assessed at baseline, 1 month, 6 months and 12 months.

To calculate the DYS, color-coded tissue Doppler imaging was acquired in the apical four-, two- and apical long-axis views after optimizing pulse repetition frequency, color saturation, and sector size and depth with minimal frame rate >100 Hz [31]. At least 5 consecutive beats were stored, and images were analyzed offline with customized software (EchoPac-PC, Version 7.0.0, Vingmed, General Electric, Norway). Myocardial velocity (sampling window: 6×12 mm) curves were reconstituted in each segment of the six basal, six mid-LV segmental model. Dyssynchrony Index was calculated from the standard deviation of the time to peak systolic velocity during the ejection phase of the 12 LV segments was measured [32,33]. In patients with high degree of atrioventricular block, the difference of R–R interval was less than 10% in the cardiac cycles selected in different apical views for measuring the time domain so as to minimize the impact of the difference in heart rate. A cutoff value of Dyssynchrony Index of >33 ms has been validated previously to signify significant DYS [10,31–33].

During offline analysis by the echocardiographic core laboratory, images from different time points and patient groups were arranged in a scrambled order, and were then analyzed by experienced doctors in a blinded fashion. The echocardiographic specialists responsible for the analysis were unaware of the assigned treatment. Dyssynchrony Index assessed by tissue Doppler imaging was evaluated by two independent observers blinded to LV volumes and functions of all the time points. Inter- and intra-observer variability for measurement of LV ejection fraction, LV end-systolic volume and Dyssynchrony Index were 3.9% and 4.2%, 6.7% and 6.5%, as well as 4.7% and 3.2% respectively as validated previously [26,31].

2.4. Study end-points

The two co-primary end-points were LV systolic function at 12 months as assessed by LV ejection fraction, and LV remodeling as assessed by LV end-systolic volume. Early change of Dyssynchrony Index was a pre-specified analysis, which was measured at 1 month follow up. In order to assess the impact of development of early DYS (defined as Dyssynchrony Index >33 ms) on long-term LV systolic function, a reduction of LV ejection fraction ≥5% at 12 months was predefined as a significant [26]. The prespecified echocardiographic secondary end-points were also measured. Mitral inflow velocities and spectral pulse-wave TDI at septal mitral annulus were obtained and mitral E/E′ was therefore generated. Mitral regurgitation was calculated by jet area as percentage of left atrial area [34] and myocardial performance index were assessed se previously described [35].

2.5. Statistical analysis

Primary analysis was based on intention-to-treat and drop outs were analyzed according to last-observation-carried-forward principle. A two-sided t-test was used to examine for a difference in the pre-specified end-points between groups at baseline and at the 12-month visit. For analysis when the assumption of normality was violated, a non-parametric test (Mann–Whitney test or Wilcoxon Signed Rank Test) was performed. Comparison of the prevalence of patients who developed significant systolic dyssynchrony in the RVA and BiV pacing groups as well as prevalence of patients who had reduction of ejection fraction ≥5% between groups were performed by Pearson Chi-square test. In order to assess the impact of DYS on LV systolic function at 12 months, patients were stratified by whether they develop significant LV DYS at 1 month. Repeated measurements of LV end-systolic volume, LV ejection fraction between difference time points were measured with Greenhouse-Giesse adjustment made when sphericity of data violated according to Mauchly's test. Univariate and stepwise multiple logistic regressions were used to examine for independent predictors of significant reduction in LV ejection fraction ≥5% at 12 months. Data were analyzed by dedicated software (SPSS Version 17.0, SPSS Inc., Chicago, Illinois, United States). A p value<0.05 was considered statistically significant.

3. Results

3.1. Patients

A total of 177 patients were recruited into the study, with 89 randomized to BiV pacing and 88 to RVA pacing. Four patients were not included in the analysis at 12 months as 2 patients refused to complete a 12-month clinic visit (1 from each group, who remained well clinically at 12 months), 1 death in the RVA arm and 1 patient in the BiV arm had inadequate image quality for echocardiographic analysis. As published previously, the RVA pacing group had significant reduction of LV ejection fraction and increase in LV end-systolic volume at 12 months, but was unchanged in the BiV pacing group, leading to a significant difference of LV ejection fraction of 7.4% and LV end-systolic volume of 8.1 ml between the two groups (both p<0.001) [26].

3.2. Impact of systolic dyssynchrony on primary end-points

At 1 month, Dyssynchrony Index was significantly higher in the RVA pacing than BiV pacing group (34±14 vs. 24±12 ms, p<0.001) though it was similar at baseline (26±11 vs. 30±14 ms, p = 0.06). At baseline, DYS was present in 19.1% (n = 16) of patients in RVA pacing group and 22.7% (n = 20) in the BiV pacing group ($\chi^2 = 0.244$, p = 0.721), while at 1 month it was significantly increased to 52.3% (n = 46) in the RVA pacing group and remained low (14.6%, n = 13) in the BiV pacing group ($\chi^2 = 28.25$, p<0.001). At 12 months, Dyssynchrony Index was consistently higher in the RVA than BiV pacing group (37±14 vs. 27±9 ms, p<0.001). As a result, the prevalence of DYS was significantly higher in the RVA than the BiV pacing group (62.0% vs. 6.8%, $\chi^2 = 25.45$, p<0.001). Interestingly, in BiV pacing group, DYS disappeared in 7 patients at 12 months in