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Less is more: Can we achieve cardiac resynchronization with 2 leads only?☆

Mauro Biffi [a,*], Giulia Massaro [a], Andrea Candelora [a], Andrea Angeletti [a], Cinzia Valzania [a], Cristian Martignani [a], Diego Grassini [b], Igor Diemberger [a], Matteo Ziacchi [a]

[a] Azienda Ospedaliero-Universitaria di Bologna, Policlinico S.Orsola-Malpighi, Università di Bologna, Italy
[b] Biotronik Italia, Italy

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ABSTRACT

Background: We compared clinical and technical outcome of CRT recipients treated either with a conventional 3 leads (3L) CRTD or with the new 2 leads (DX) CRTD that enables atrial signal detection by a floating dipole built on a pentafilar RV lead.
Methods: Echocardiography and cardiopulmonary exercise tests were repeated either before CRTD implantation and between 6 and 12 months follow up in consecutively implanted patients who had a resting heart rate > 40 bpm at maximum tolerated beta-blocker dosage. HF status, reverse LV remodeling, exercise tolerance and chronotropic incompetence were assessed at 12 months FU. Device diagnostics were obtained twice yearly until December 2016.
Results: 37 patients aged 66 (58–73) years were consecutively implanted in 2013–2014 according to current guidelines, 25 with a 3L CRTD and 12 with a DX CRTD. Beta-blocker dosage was similar, and no difference between the 2 groups was observed in terms of NYHA class improvement, LV reverse remodeling, peak cardiopulmonary performance and presence of chronotropic incompetence at 12 months follow up. There was no difference in: amount delivered CRT; occurrence of VT/VF; occurrence of AT/AF. No patients developed need of atrial stimulation at 3-years FU. Atrial undersensing never occurred in any patient, whereas Far-field R-wave oversensing was more common in 3L patient than in DX patients (8/25 vs none, $P < 0.05$). P wave amplitude was greater in DX vs 3L patients [5.1(3.7–9.2) vs 2.9(2–3.9) mV, $P < 0.01$].
Conclusion: CRT can be achieved with two leads-only in the majority of patients, provided that indication to atrial stimulation is ruled out.

1. Introduction

Cardiac Resynchronization Therapy is usually delivered by devices equipped with 3leads to enable P wave synchronized biventricular or left ventricular (LV) stimulation [1]. Whereas atrial sensing is pivotal to ensure the optimal timing of ventricular systole at the most effective LV filling [2], the role of atrial pacing as rate support is uncertain [3–5].

Indeed, in the 2012 EHRA/HRS guidelines the recommendations on CRT programming suggest a lower rate 35–40 bpm to enhance VDD mode behavior and to avoid the potentially confounding effect of atrial stimulation support [6].

The aim of this study was to evaluate the possibility to deliver CRT with two leads-only devices that feature atrial detection by a floating atrial dipole on the RV lead, in comparison with conventional CRT systems. The reliability of the systems was evaluated in terms of tracking of sinus P waves, amount of delivered CRT, atrial arrhythmia detection, cardiopulmonary exercise performance, NYHA class, and LV reverse remodeling.

2. Methods

This investigation was a prospective single center study involving parallel cohorts. We aimed to investigate the reliability of CRT delivery by a device featuring P wave detection by a floating atrial dipole built-in the RV lead (DX) compared to a standard 3 leads (3L) CRTD device. In this perspective, both clinical data, reverse LV remodeling, and technical device performance were investigated. We also aimed to understand to what extent chronotropic incompetence (CI) is prevalent and impacts on CRT recipients. All patients enrolled in the study received a CRTD in accordance with the European Society of Cardiology and European Heart Rhythm Association guidelines. The requirement to participate to the study was to be followed at our outpatient device clinic for at least 3 years, and to undergo 2 cardiopulmonary exercise tests, before and after implantation. The study was approved by the Hospital Ethic Committee.

Echocardiography was used to measure left ventricular (LV) volumes, EF, and mitral regurgitation grade (MR) either before CRT implantation and between 6 and 12 months follow-up. Response to CRT was defined according to Ypenburg criteria: super-responders have an end-systolic volume index (ESVi) reduction ≥30%, responders have

☆ All Authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: A.O.U. di Bologna, Via Massarenti 9, 40138 Bologna, Italy.
E-mail address: mauro.biffi@aosp.bo.it (M. Biffi).

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an ESVi reduction 15 to 29%, non-responders have an ESVi reduction ≤14%, and negative responders have an increase of ESVi [7]. The reproducibility of Echocardiographic measurements in our laboratory has been previously reported [8]. In addition a cardiopulmonary stress test was performed before the device implantation and between 6 and 12 months follow-up, to evaluate patients performance and chronotropic competence. The cardiopulmonary stress test was performed using a specific protocol for heart failure patients, with a 10-Watt workload increase every 60 s by cycle ergometry (VmaxEncore29S, SensorMedics, Palo Alto, California). Workload was computer-controlled during continuous ECG monitoring, heart rate (HR) and blood pressure were sampled during each exercise phase. The test was conducted until muscular exhaustion but for the onset of severe symptoms or sustained tachy-arrhythmias. Atrial and right ventricular sensing amplitude were measured at each stage of the cardiopulmonary test: rest, peak of exercise, recovery at 2 min after exercise. Chronotropic competence was calculated as (peak HR – maximum predicted HR)/maximum predicted HR, and as heart rate reserve (peak exercise HR - resting HR) / (maximum predicted HR - resting HR). We evaluated how many patients had chronotropic incompetence at arbitrarily accepted level of 80% and 70%, respectively, and by a heart rate reserve (HRR) < 62% on beta blockers or <80% off beta blockers [9,10]. After at least 6 months follow-up, patient were reevaluated to assess the response to resynchronization therapy: ESVi, NYHA class, ejection fraction and cardiopulmonary stress test were compared with baseline values. Patients were not given instruction to a formal training program after CRT implantation, but were simply encouraged to increase physical activity as to achieve a normal lifestyle.

Based on our customary clinical practice, CRTD were programmed similarly to mimic VDD mode, as no patient had indication to atrial stimulation: lower rate 30 to 40 bpm, upper rate 150 bpm. VT cutoff rate was set at 170 bpm (minimum detection 48 intervals), and VF cutoff was set 209–214 bpm (detection 24/30 intervals for DX, 30/40 for 3L). LV or Biventricular stimulation triggered by sensing of intrinsic ventricular events and response to sensed atrial fibrillation were turned off in all the patients.

CRT was delivered by Echo-optimized programming (best LV filling time) testing either LV-only or biventricular stimulation by the iterative method at different AV and VV delays following our previous experience [8].

The DX lead consisted of an active fixation 5-conductors single-coil lead, with a ventricular pacing/sensing dipole, and an atrial sensing dipole (available in two lengths, respectively 15 cm and 17 cm from the ventricular tip) [11]. The location of the atrial dipole occurred by probing the right atrium (RA) full length in cranial-caudal direction after screwing the ventricular tip, and was guided by the measurement of the P wave amplitude via the pacing system analyzer. Atrial dipole location was deemed acceptable at the highest P wave amplitude or when P wave amplitude was at least >0.5 mV either during normal breath or during deep breath: fluoroscopy was taken at the end of the selection process to ensure that both excessive lead coiling (by pushing the dipole to the lower RA), and excessive lead straining (by pulling the dipole to the high RA) were avoided. The arbitrary cutoff of 0.5 mV was deemed sufficient, as DX system amplifies the signal amplitude 4-fold at minimal compromise with background noise amplification [11].

2.1. Statistical analysis

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (25th and 75th percentiles) for non-normally distributed variables, or percentages for binary variable. Missing data were not replaced; all available data were used for sample distribution evaluation. Normality was checked with the Shapiro-Wilks test and the Mann-Whitney Test was used for inter-individual comparisons of continuous variables, when normality was rejected. Categorical variables were compared with the Fisher's exact test. The Logistic regression was used to conduct the univariate analysis of predictors of non-response to the CRT therapy; the most significant three variables were included in the multivariate logistic regression model due to the presence of 16 positive cases. In order to model changes in cardiac volumes and oxygen consumption from baseline to 6 months, linear mixed models were used hierarchically over responder/non-responder random coefficients with CRT as fixed effect. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using the version 11E of STATA software (StatCorp LP, Texas, USA).

3. Results

In the years 2013–2014 all consecutive CRT recipients were screened for participation to the study: 37/154 agreed. Among the others, 104 participated into other clinical studies, 11 preferred to be followed at the closer/referring clinical facility, and 2 had indication to atrial stimulation because of severe sinus bradycardia alternating with junctional rhythm at rest below 39 bpm on low-dose bisoprolol (≤1.875 mg/daily). Overall, indication to atrial stimulation was observed in 2/154 (1.2%) of CRT recipients (27 CRTP, 127 CRTD) along 2 years. The baseline clinical characteristics of the 37 enrolled patients are reported in Table 1. No difference was observed between the 2 groups, with the exception of a higher prevalence of female's in the DX group, stemming from the non-randomized nature of the study. Ischemic etiology of heart failure was equally represented despite the sex difference (Table 1).The 3L patients received a Medtronic CRTD (Medtronic Inc., Minneapolis, MN), whereas the DX patients received a Biotronik LUMAX 740 HFT equipped with a Protego ProMRI S DX 65/15 RV lead to detect the atrial signal (Biotronik 414064, Berlin, Germany). EKG, echocardiographic data and exercise test at baseline were similar across the study group but for a shorter P wave duration in DX patients (Table 1).

Rate-lowering drugs were used similarly in the 2 groups (Table 1): 2 patients in the DX group were off beta-blockers because of asthma (1 on ivabradine) and of hypotension (1 on amiodarone for paroxysmal AF), whereas 1 patient in the 3L group did not take beta blockers for hypotension. The average carvedilol dosage was similar in the 2 groups (Table 1), and remained unchanged at follow up. One patient in the 3L group received Amiodarone during follow up because of AF.

The average FU was 36.6 (34.7–40.9) months and 34 (28.2–35.9) months, respectively in the 3L and in the DX group; there were 2 deaths and 1 heart transplantation in the 3L group vs 0 deaths and Heart transplantation in the DX group. One patient underwent aortic valve replacement at 20 months FU, and one is on waiting list for heart transplantation in the DX group. Four patients (10.8%) received ICD therapy during FU: 1 (ATP + shock) in the DX group (waiting list for heart transplantation); 3 in the 3L group, 1 ATP only (transplanted) and 2 ATP + shock (both dead because of pump failure associated to acute comorbidities). Permanent Atrial Fibrillation (AF) developed in 1 patient and Paroxysmal AF occurred in 5 in the 3L group, whereas 1 patient in the DX group underwent electrical cardioversion because of persistent AF and 1 had paroxysmal AF. Re-interventions occurred in 2 patients because of LV lead dislodgement (5.4%), 1 patient in each group: both were managed by repositioning with lead stabilization [12].

LV reverse remodeling was assessed by echocardiography at FU, and was comparable in the 2 groups (Table 2); DX patients had a greater reduction of end-systolic volume index (ESVi) and a greater improvement of EF (Table 2). NYHA class improved similarly in both groups: a reduction of at least 1 NYHA class was respectively observed in 19/25 (76%) of 3L and in 9/12 DX (75%) patients, whereas an unchanged or worsened NYHA class was observed respectively in 6/25 (24%) of 3L and in 3/12 (25%) of DX patients (P = NS). Male sex was the only independent negative predictor of reverse LV remodeling (Table 2).

The cardiopulmonary test at FU was similar between the two groups (Table 2): IC prevalence was similar, as shown in Fig. 1, panel A–B.

LV reverse remodeling did not appear associated to an increased peak oxygen consumption at cardiopulmonary exercise test (Fig. 1, panel C–D).

Owing to the different signal amplification and filtering, P wave amplitude and ventricular R wave amplitude were superior in DX group than 3L group, respectively, both at rest and during exercise (Table 2).

Device diagnostics at last FU visit detected significant differences over the lifetime activity: the DX group had a lower incidence of far-field R-wave oversensing (Table 3), whereas amount of delivered CRT and PVCs (that might be a hint of P wave undersensing) were comparable in the 2 groups (Table 3). The possibility to achieve atrial stimulation in different body positions was observed in 10/12(83%) DX patients at last FU visit (Table 3). CRT was delivered by Echo-optimized programming (best LV filling time) in LV-only stimulation in 20/37 patients (54%), 6 in the DX group (50%) and 14 in the 3L group (56%), whereas the other 17 patients had Biventricular stimulation with varying V—V delays.

4. Discussion

In this study we observed that CRT can be delivered either with a conventional 3L or with a 2 leads DX system, owing to a reliable atrial signal detection over long term. Atrial stimulation because of clinically meaningful sinus node dysfunction or chronotropic incompetence was

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