Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: Twelve-month follow-up study

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BACKGROUND Cardiac resynchronization therapy (CRT) with multipoint left ventricular (LV) pacing (MultiPoint™ Pacing [MPP], St. Jude Medical) improves acute LV function and LV reverse remodeling at 3 months.

OBJECTIVE The purpose of this study was to test the hypothesis that MPP can also improve LV function at 12 months.

METHODS Consecutive patients receiving a CRT implant (Unify Quadra MP™ or Quadra Assura MP™ CRT-D and Quartet™ LV lead, St. Jude Medical) were randomized to receive pressure–volume (PV) loop optimized biventricular pacing with either conventional cardiac resynchronization therapy (CONV) or MPP. CRT response was defined by a reduction in end-systolic volume (ESV) $\geq$15% relative to BASELINE as determined by a blinded observer and alive status.

RESULTS Forty-four patients (New York Heart Association class III, ejection fraction [EF] 29% $\pm$ 6%, QRS 152 $\pm$ 17 ms) were enrolled and randomized to either CONV (N = 22) or MPP (N = 22). During the observation period, 2 patients died of noncardiac causes and 2 patients were lost to follow-up. After 12 months, 12 of 21 patients (57%) in the CONV group and 16 of 21 patients (76%) in the MPP group were classified as CRT responders (P = .33). ESV reduction and EF increase relative to BASELINE were significantly greater with MPP than with CONV (ESV: median −25%, interquartile range [IQR] [−39% to −20%] vs median −18%, IQR [−25% to −2%], P = .03; EF: median +15%, IQR [8% to 20%] vs median +5%, IQR [−1% to 8%], P < .001).

CONCLUSION Sustaining the trend observed 3 months postimplant, PV loop-guided multipoint LV pacing resulted in greater LV reverse remodeling and increased LV function at 12 months compared to PV loop-guided conventional CRT.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Cardiac resynchronization therapy response; Multipoint pacing

ABBREVIATIONS **CONV** = conventional cardiac resynchronization therapy; **CRT** = cardiac resynchronization therapy; **CS** = coronary sinus; **dP/dt** = rate of pressure change; **EF** = ejection fraction; **ESV** = end-systolic volume; **IQR** = interquartile range; **LBBB** = left bundle branch block; **LV** = left ventricle; **MPP** = MultiPoint™ Pacing; **NYHA** = New York Heart Association; **PV** = pressure–volume; **RV** = right ventricle

Introduction

Cardiac resynchronization therapy (CRT) provides significant long-term benefits to patients with moderate-to-severe heart failure, prolonged QRS duration, and reduced ejection fraction (EF).[1–5] However, conventional therapy is partly limited by the up to 40% of patients who fail to clinically respond positively.[6,7]

Multipoint left ventricular (LV) pacing in a single coronary sinus (CS) branch (MultiPoint™ Pacing [MPP], St. Jude Medical, Sylmar, CA) from a quadripolar LV lead is 1 strategy to improve CRT response.[8] Initial experience has shown that MPP provides acute benefit to LV dP/dt_{Max},[9] LV dyssynchrony,[10] LV peak radial strain,[11] LV systolic and diastolic pressure–volume (PV) loop parameters,[12] LV

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electrical activation,[13] and improves LV function at 3 months.[14] However, the long-term effects of MPP remain unknown. In this study, we evaluated the 12-month outcomes between patients randomized to receive either hemodynamically optimized MPP or similarly optimized conventional biventricular pacing.

Methods

See the Online Supplement for additional details.

Study population

This study enrolled consecutive patients who met the inclusion and exclusion criteria at a single investigational center between April 2012 and November 2012. The study protocol was approved by the local ethics committee. and the investigation conformed to the principles outlined in the Declaration of Helsinki. Inclusion criteria were a CRT implant indication approved by ESC/EHRA guidelines[15] and the ability of the patient to provide informed consent. Exclusion criteria were New York Heart Association (NYHA) class IV, myocardial infarction within 40 days before enrollment, documented Cheyne–Stokes respiration, cerebrovascular accident or transient ischemic attack within 3 months before enrollment, cardiac surgery or coronary revascularization procedure within 3 months before enrollment or scheduled in the following 7 months, intravenous inotropic support in the last 30 days, age younger than 18 years, and pregnancy.

Implant procedure

A CRT device (Unify Quadra MP™ or Quadra Assura MP™, St. Jude Medical) with the ability to deliver MPP (ie, 2 LV pacing pulses [LV1 and LV2] and right ventricular [RV] pacing pulse with programmable delays between pacing pulses [LV1–LV2 and LV–RV delays]) was implanted in patients under conscious sedation. Conventional RV and right atrial leads and a quadripolar LV lead (Quartet™ LV lead, St. Jude Medical) were placed according to standard practice. The LV lead with electrodes named D1, M2, M3, and P4 (distal to proximal) was targeted to a lateral, posterolateral, or anterolateral branch of the CS. The distal electrode was targeted to an apical or midventricular position, allowing for greater lead stability and the ability to pace basally with the proximal electrodes.

Selection of LV pacing vectors

After device implant and recording of hemodynamic measurements, patients were randomized in a 1:1 ratio to either the conventional cardiac resynchronization therapy (CONV) group or the MPP group according to randomization letters provided to the center. Before patients left the hospital, their devices were programmed to the configuration in their randomly assigned pacing mode (CONV or MPP) that produced the largest relative increase in dP/dt_{Max} during intraoperative PV loop measurements. Device settings determined by hemodynamic measurements for patients in the MPP group were the first LV pacing vector (LV1), the second LV pacing vector (LV2), the delay from LV1 to LV2 pacing (LV1–LV2 delay), and the delay from LV2 to RV pacing (LV2-RV delay) and for patients in the CONV group was the LV pacing vector. Patients remained blinded to their group assignment throughout the 12-month observation period.

Echocardiographic measurements and clinical examination

Patients underwent echocardiographic and clinical evaluation before implant (BASELINE) and again 3 months and 12 months after implant. LV end-systolic volume (ESV) and end-diastolic volume were measured, and the EF derived, by an observer blinded to the patients' pacing configuration with a transthoracic echocardiography system (iE33, Philips, Amsterdam, The Netherlands). Patients were considered to be responders to CRT at the 12-month follow-up visit if they (1) were alive and (2) experienced a reduction in ESV $\geq$15% relative to BASELINE.[16,17] A retrospective analysis additionally divided patients into super-responders with reduction in ESV $\geq$30% relative to BASELINE and negative responders with increase in ESV relative to BASELINE or death during the observation period.[18]

Study end-points

The primary end-point of the study was the change in ESV and EF from BASELINE to 12 months in the MPP group vs the CONV group. *Post hoc* subgroup analyses of echocardiographic and clinical changes were conducted based on patient heart disease etiology (ischemic or nonischemic) and QRS morphology (left bundle branch block [LBBB] or non-LBBB).

Statistical analysis

For changes in echocardiographic measurements, median and interquartile range (IQR) are reported, and comparisons between groups were performed with the Mann–Whitney *U* test. Other continuous variables are expressed as mean ± SD and were compared with the unpaired *t* test. Categorical variables were compared with the Fisher exact test. $P < .05$ was considered significant.

Results

Study population, enrollment, randomization, and follow-up

Forty-four patients were enrolled and successfully implanted with the MPP-enabled CRT device and quadripolar LV lead. All patients underwent PV loop measurements and were randomized to the CONV group or the MPP group. During the 12-month observation period, 2 patients in the MPP group died of noncardiac causes (1 acute renal failure and 1 complications from diabetes) and 2 patient from each group was lost to follow-up (Figure 1). Of the remaining patients, the mean follow-up period was 368 ± 13 days in the MPP group and 368 ± 9 days in the CONV group ($P = .90$).