Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year

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BACKGROUND Approximately one-third of the patients with heart failure (HF) treated with cardiac resynchronization therapy (CRT) fail to respond. Positioning the left ventricular (LV) pacing lead in the area of the latest electrical delay may improve the response to CRT. Multipoint pacing (MPP) of the LV has been shown to improve the acute hemodynamic response.

OBJECTIVE The purpose of this study was to test the hypothesis that patients treated with MPP in whom LV pacing location is optimized have better long-term clinical outcomes than do patients treated with conventional CRT.

METHODS We evaluated the echocardiographic and clinical response of 110 patients with HF treated for nearly 1 year with either conventional CRT (standard [STD] group, n = 54, 49%), CRT with hemodynamic and electrical optimization of the LV pacing site (optimized [OPT] group, n = 36, 33%), or OPT combined with MPP (OPT + MPP group, n = 20, 18%). Responders were classified in terms of reduction in end-systolic volume index ≥15%, reduction in New York Heart Association (NYHA) class ≥1, and Packer score variation (NYHA response with no HF-related hospitalization events or death).

RESULTS In STD, OPT, and OPT + MPP groups, 56%, 72%, and 90% of patients, respectively, were end-systolic volume index responders ($P = .004$) and 67%, 78%, and 95% were NYHA class responders ($P = .012$); 59%, 67%, and 90% of patients exhibited a 1-year Packer score of 0 ($P = .018$). These trends remained significant after adjustment for confounding factors by multivariate logistic analysis.

CONCLUSION Combining MPP with optimal positioning of the LV lead on the basis of electrical delay and hemodynamics enhances reverse remodeling and improves clinical outcomes beyond the effect due to conventional CRT.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Multipoint pacing; Hemodynamic response; Left ventricular pacing; Electrical delay

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Introduction

Cardiac resynchronization therapy (CRT) involves electrical stimulation of the left ventricle (LV) of patients with heart failure (HF). Commonly applied through a tributary of the coronary sinus, it attempts to restore ventricular synchrony and improve hemodynamics. CRT has been shown to reduce HF-related morbidity and mortality and to improve quality of life.[1–3] However, in approximately one-third of the patients with HF, CRT fails to improve clinical parameters, and in up to 50% of the treated patients it does not reverse LV remodeling (decrease in LV end-systolic volume [ESV]).[4,5]

Efforts to address CRT nonresponse have included optimizing the LV pacing site. While attempts have been made to identify superior LV pacing sites on the basis of anatomy alone, but consistent correlations with CRT response have not emerged across patient populations.[6] Addressing electrical dyssynchrony directly by pacing at the latest activated LV site, however, seems promising. Previous studies,[7,8] including ours,[9] have demonstrated a correlation between the intrinsic electrical delay of an LV

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pacing site and subsequent improvement in hemodynamics and reduction in electrical dyssynchrony. Specifically, positive correlations have emerged between Q-LV (LV lead electrical delay) and both LV dP/dt_{max} (maximum rate of increase in LV pressure) and QRS narrowing.[9] Moreover, pacing at sites with longer Q-LV is linked to better long-term outcome.[7,10,11]

The recently introduced quadripolar leads simplify pacing site selection by allowing the LV pacing site along a target vein to be remotely programmed without lead repositioning. Additional acute hemodynamic improvement has been achieved with the introduction of multipoint pacing (MPP) of the LV,[12–17] whereby multiple LV sites along the single quadripolar lead are stimulated in order to capture a broader region of excitable myocardium.[18] It has been demonstrated that MPP elicits a greater hemodynamic improvement than does conventional CRT (pacing single sites at the right ventricular [RV] and the LV lead) in terms of LV dP/dt_{max},[12,13] pressure-volume loop metrics,[14] LV radial strain,[15] LV outflow tract velocity-time integral,[16] and impedance cardiography.[17]

However, little information is available on the long-term benefits of MPP and there is conflicting evidence as to whether the acute hemodynamic response to CRT predicts long-term clinical outcome.[19,20] We therefore aimed to investigate the long-term effects of optimized LV lead placement, both alone and in combination with MPP. To this end, we analyzed the 1-year follow-up data on patients treated in our hospital and compared echocardiographic and clinical improvements in 3 patient groups: those undergoing conventional CRT, those with optimized lead placement (lead at the longest Q-LV), and those in whom optimized lead placement was combined with MPP.

Methods

Study design

This investigation was a retrospective single-center study involving nonparallel cohorts. The study protocol was approved by the local ethics committee and adhered to the principles outlined in the Declaration of Helsinki. All patients enrolled in the study were indicated for CRT in accordance with the European Society of Cardiology/European Heart Rhythm Association guidelines[21] and provided written informed consent to use their clinical data.

The following baseline demographic characteristics, comorbidities, and HF status metrics were recorded before CRT implantation: age, sex, New York Heart Association (NYHA) class, LV ejection fraction, end-diastolic volume index (EDVi), end-systolic volume index (ESVi), QRS duration, and history of ischemic cardiomyopathy, left bundle branch block, percutaneous coronary intervention (PCI), coronary artery bypass graft, valvular disease, acute myocardial infarction, diabetes, hypertension, atrial fibrillation, and renal failure (glomerular filtration rate <30 mL/min). EDVi and ESVi were calculated as the ratio of EDV and ESV to body surface area, respectively. Echocardiographic parameters and inter- and intraobserver variability in our center have already been described.[22]

QRS morphology was classified according to American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society guidelines.[23] Because all these measurements had been taken as part of standard clinical care in our center and before the study groups were formed, the researchers performing the analyses were blinded to the group to which a patient belonged.

In accordance with our standard implantation procedure, the RV lead was implanted in the mid-septum and the atrial lead was implanted in the right atrial appendage. A previously described telescopic approach[24] was used for cannulation of the coronary sinus and subcannulation of all suitable collateral veins; this approach allows continuous selective navigation with angiographic visualization. All veins that were actually cannulated and then targeted with the LV pacing lead were defined as available veins. We did not collect data on veins that were visualized but not cannulated. LV pacing sites were anatomically classified by using a system previously established by Singh et al.[25] Briefly, on segmenting the left anterior oblique (short-axis) fluoroscopic view, the pacing site was classified as anterior, anterolateral, lateral, posterolateral, or posterior; on segmenting the right anterior oblique (long-axis) fluoroscopic view, the pacing site was classified as basal, mid, or apical.

After nearly 1 year of follow-up, patients were reevaluated to determine the chronic response to resynchronization therapy; ESVi, NYHA class, and Packer score[26] were compared with the preimplantation baseline values. “ESVi responders” were those with a reduction in ESVi of $\geq 15\%$[27]; “NYHA responders” were those with a reduction in NYHA class of ≥ 1; and “Packer responders” were those exhibiting a Packer score of 0, indicating a reduction in NYHA class with no HF-related hospitalization events or death in the year before the follow-up examination.

Cohort description

Three groups of patients were compared.

The conventional CRT group was composed of 54 consecutive patients with HF with conventional CRT devices equipped with bipolar LV leads without any optimization (standard [STD] group). The STD group received CRT treatment between January 2011 and March 2012. According to our practice,[24] coronary sinus angiography was performed to visualize a target vein in the LV free wall, preferably in the lateral or posterolateral region. The target vein was chosen according to the angle, bifurcation, and caliber of the vessel; the anatomical position along the LV free wall (for lead stability); and the electrical parameters (pacing threshold and phrenic nerve stimulation).

The second CRT group was composed of 36 patients with HF with CRT devices equipped with either bipolar or quadripolar LV leads, the sites of which were optimized on the basis of LV dP/dt_{max} and Q-LV (optimized [OPT] group). OPT group patients underwent implantation between