Cardiac resynchronization therapy improved the clinical outcomes in pacemaker patients upgraded to biventricular device

Han JIN, Wei HUA*, Li-Gang DING, Jing WANG, Hong-Xia NIU, Min GU, Cong XUE, Shu ZHANG

The Cardiac Arrhythmia Center, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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The right ventricular pacing (RVP) is the standard treatment for patients with severe bradyarrhythmias; however, it may cause and exacerbate heart failure symptoms in a long run under some circumstances.[1] In fact, significant left ventricular (LV) systolic dysfunction and symptomatic heart failure (HF) is commonly found in patient population with pacemaker implantations.

Cardiac resynchronization therapy (CRT) has been demonstrated to be an effective therapy to reduce morbidity and mortality in patients with advanced congestive heart failure in a series of large randomized trials of CRT.[2] However, patients with chronic RVP upgraded to CRT were largely excluded from these trials.

Recent prospective and retrospective studies[3,4] have supported that upgrading conventional RVP to biventricular (BiV) pacing by means of CRT in pacing-dependent patients with heart failure can improve their electrical and mechanical intra- and intra-ventricular synchrony and functional status.[5,6] However, the long-term effect of CRT on these patients has not yet been thoroughly assessed. We aim to evaluate the clinical outcomes of chronic RV paced patients with heart failure who underwent CRT device upgrade compared to those who did not.

The study was a prospective nonrandomized multiple-center study which involved 21 clinical centers all over mainland, China. The patients were predominantly RV paced (defined as no less than 80% pacing on the last two interrogations of the device before enrollments), and had evidence of moderate to severe heart failure [New York Heart Association (NYHA) class III-IV] despite optimized tolerated medical therapy, LV systolic dysfunction [left ventricular ejection fraction (LVEF) < 35%], and a prolonged QRS complex greater than 120 ms. Patients with a recent myocardial infarction or revascularization (< 3 months) as well as those with a reversible cause of heart failure (e.g., myocarditis) were excluded from the study. Patients with either ischemic or non-ischemic cardiomyopathy were studied. In the study, the diagnosis of ischemic cardiomyopathy was made if systolic dysfunction was associated with a history of myocardial infarction.

From February 2008 to December 2010, a total of 105 patients with prior pacemaker implantation who met the study inclusion and exclusion criteria were identified due to the battery depletion or for new or worsening HF symptoms. Among them, 35 patients accepted the CRT implantation per their own willingness and were enrolled into the CRT upgrade group. The rest of 70 patients refused to accept CRT implantation due to various concerns and were enrolled into the continuing RVP or control group. All patients enrolled were predominantly RV paced with a mean RVP length of 7.9. RVP site was confirmed by X-rays and electrocardiography. In the CRT upgrade group, 27 patients were pacing at RV apical site and eight patients were pacing at other locations, such as septal. In the RVP group, 43 patients were at RV apical site, 17 were at other locations and the related information was unknown for 10 patients.

The baseline clinical assessment, including the 6 min walk test, echocardiography and the history of medical record, were measured on the day prior to CRT implantation in the CRT upgrade group or right after signed patient informed consent in RVP group. Information on hospitalization and the cost of related treatments in the past six months prior to the study enrollment were also documented. The same clinical evaluation was repeated at 7 days, 3 month, 6 month and 12 month. Echocardiography examinations were performed at the individual center per the same measurement method. Four example, the conventional echo parameters, such as LV end-systolic volume (LVESV), end-diastolic volume (LVEDV), and LVEF were assessed using Simpson’s equation from the apical 4-chamber and 2-chamber views.

In the CRT upgrade group, CRT implantation was per-
formed using standard techniques. Acceptable parameters were defined as a LV pacing threshold less than 3.5 V with absence of phrenic nerve stimulation from the same site at 10 V. All patients had an LV lead with acceptable pacing parameters at appropriate lateral or anterolateral location unless such locations were not available via trans-venous route. Either CRT-P device (24 cases) or CRT-D device (11 cases) were used in the CRT upgrade group per the history of ventricular arrhythmias. The CRT optimizations were performed under echocardiographic guidance at each individual study center.

Quantitative values were expressed as means with standard deviations and compared using the paired Student t-test. A two tailed $P < 0.05$ was considered statistically significant, while $P$-value between 0.05 and 0.15 indicated a statistical trend.

The patient population consisted of 76 male and 29 female subjects with an average age of 66.1 ± 12.1 years and average NYHA class 3.12 ± 0.38. The patient population had much less ischemic ($n = 28$) etiology than non-ischemic etiology ($n = 77$). QRS duration in these patients ranged from 120 to 260 ms and mean LVEF was 29.0% ± 5.0%. All of them were in greater than 80% paced rhythm and under medical therapy. The groups were well matched for age, gender and ischemic aetiology (Table 1). During the 12 month follow up, QRS duration in the CRT-upgrade group decreased significantly from the baseline 189.3 ± 33.4 ms to 150.30 ± 29.3 ms ($P < 0.001$), while the RVP group had no significantly change from the baseline 178.3 ± 38.4 ms to 172.1 ± 29.1 ms ($P = 0.24$). At the end of 12 months, LVEF was significantly improved in the CRT-upgrade group (45.2% ± 11.1%) compared to 32.4% ± 8.5% in the RVP group ($P < 0.001$), while no significant difference ($P = 0.31$) was found at the baseline 28.1% ± 5.3% in the RVP group and 30.7% ± 4.3% in the CRT upgrade group (Table 2). The NYHA functional class was significantly improved in the BiVP group compared to the RVP group (2.23 ± 0.90 vs. 3.02 ± 0.71; $P < 0.001$), while the baseline was 3.15 ± 0.36 in the RVP and 3.07 ± 0.25 in the BiVP ($P = 0.27$).

CRT major clinical trials demonstrated that CRT reduces symptoms and mortality in patients with severe chronic heart failure and intra- and inter-ventricular dyssynchrony due to intrinsic left bundle branch block (LBBB); however, patients with HF and chronic RVP, who often meets the current criteria for CRT and has an LBBB pattern on the electrocardiograph when paced, were largely excluded from these trials. The present study has shown that in patients with heart failure who are chronically RV paced, upgrading to CRT substantially benefited patient in terms of symptoms and hospitalization compared to those with status quo. These benefits were associated with the statistically improved LVEF and shorten QRS duration.

Several studies have reported on the effects of upgrading

| Table 1. Baseline characteristics of the study population. |
|---------------------------------------------------------|
| All (n = 105) | Control (n = 70) | CRT upgrade (n = 35) |
|---------------|-----------------|---------------------|
| Age, yrs      | 66.1 ± 12.1     | 65.4 ± 11.5         | 67.6 ± 13.2         |
| Male          | 76 (72%)        | 51 (73%)            | 25 (71%)            |
| Ischemic aetiology | 28 (27%) | 18 (26%)            | 10 (29%)            |
| NYHA class    | 3.12 ± 0.38     | 3.15 ± 0.36         | 3.07 ± 0.25         |
| Medication    |                 |                     |                     |
| Diuretics     | 97 (92%)        | 68 (97%)            | 29 (83%)            |
| ACE-I or ARB  | 94 (90%)        | 65 (93%)            | 29 (83%)            |
| β-blockers    | 74 (70%)        | 51 (73%)            | 23 (66%)            |
| ECG variables |                 |                     |                     |
| QRS duration, ms | 181.4 ± 33.8   | 178.3 ± 38.4        | 187.7 ± 32.7        |
| LVEF          | 29.0% ± 5.0%    | 28.1% ± 5.3%        | 30.7% ± 4.3%        |

Data are presented as mean ± SD or n (%). ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; LVEF: left ventricular ejection fractions.

| Table 2. Comparison NYHA, LVEF and QRS duration in the 12 month follow up. |
|-------------------------------------------------|
| LVEF | Control (RVP) | CRT-upgrade |
|------|---------------|-------------|
| Baseline | 12 months | Baseline | 12 months |
| LVEF | 28.1% ± 5.3% | 32.4% ± 8.5% | 30.7% ± 4.3% | 45.2% ± 11.1% |
| QRS, ms | 178.3 ± 38.4 | 172.1 ± 29.1 | 189.3 ± 33.4 | 150.30 ± 29.3 |
| NYHA | 3.15 ± 0.36 | 3.02 ± 0.71 | 3.07 ± 0.25 | 2.23 ± 0.90 |

Data are presented as mean ± SD. CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fractions; RVP: right ventricular pacing.
CRT from chronic RVP in either acute setting or in the short term. Other studies also reported an acute increase in EF and a reduction in intraventricular mechanical delay by examining the impact of CRT upgrade on the acute echocardiographic and hemodynamic effects of BiV pacing. The data presented in the study are, in general, consistent with these literatures and provided further evidence that it is possible to partially reverse the deleterious effect of chronic RVP.

The main mechanisms of the observed benefit are believed to be similar to those involved in de novo resynchronization therapy, including the increase in AV synchrony, the decrease in the degree of mitral regurgitation, and the correction of inter- and intra-ventricular dyssynchrony. The clinical issues related to successful CRT upgrade implantation have not been assessed prospectively such as more difficult access to the coronary sinus from the right side or passage of pre-existing chronically implanted leads. In our multi center experience, all 35 cases of CRT upgrade were successful without difference in the frequency of periprocedural complications, which is contradicted with the 82% CRT upgrade success rate reported previously.

Numerous small studies demonstrated that CRT upgrades in patients with heart failure and chronic RVP result favorable short- and long-term clinical outcomes; however, the practice of CRT upgrade is not yet common. In fact, this option is listed in the ESC guidelines only as a class Ila recommendation. A large clinical trial is needed to establish the efficacy of CRT in this patient group.

In this study, the patients who received CRT upgrade were not randomized because of patient’s own economic judgments. The systemic bias could be generated because patients who received CRT upgrade might be more actively to manage his/her own disease progress. The patient sample was rather small and further division of the patient into CRT-responder or non CRT-responder was not statistically appropriated.

The present study provided evidence that upgrading RVP to BiV in patients with advanced heart failure improved the LV electrical synchrony, LV systolic function and NYHA classification.

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