Original Research

Upgrading Pacemaker to Cardiac Resynchronization Therapy: An Option for Patients with Chronic Right Ventricular Pacing and Heart Failure

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Introduction: Long-term pacing from the right ventricle (RV) has been shown to induce a deleterious effect on left ventricular function. Cardiac resynchronization therapy (CRT) is an established treatment for heart failure (HF) patients. The purpose of this study was to assess the benefit from upgrading to CRT in chronically RV-paced patients with a low left ventricular ejection fraction (LVEF<35%).

Methods: Thirty-seven HF patients (age 71.4 ± 7.7, 26 male), who fulfilled CRT indications, were included. Study subjects had undergone VVI or DDD pacemaker implantation 6.1 ± 5.7 years earlier and were referred to our centre because of worsened clinical condition or a depleted battery. Patients were assessed at baseline and six months after CRT. Evaluation included NYHA classification, functional capacity assessed by six-minute walk test (6MWT), hospitalization rate and echocardiographic assessment.

Results: Biventricular pacing was possible in 34 of the 37 cases (91.7%) who had their device upgraded to CRT-P (n=8) or to CRT-D (n=26). After the implementation of CRT the patients showed a noteworthy clinical improvement. Average NYHA class changed from 3.3 ± 0.6 to 2.5 ± 0.9 (p<0.001), 6MWT performance increased from 246 ± 105 m to 321 ± 101 m (p<0.001), while six-month hospitalization rate dropped from 1.4 ± 1 to 0.7 ± 0.8 admissions (p<0.001). LVEF increased from 26.3 ± 5.4% to 31.4 ± 6.7% (p<0.001) and left ventricular end-systolic volume changed from 134.3 ± 46 mL to 111.9 ± 41.1 mL (p<0.001). A reduction in QRS duration by 28 ms (p<0.001) was also noted.

Conclusions: RV-paced patients should be closely monitored, and upgrade to CRT should be considered promptly if they develop moderate or severe HF.

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Cardiac resynchronization therapy (CRT) is an established therapeutic option for patients with advanced congestive heart failure (NYHA III-IV), reduced left ventricular ejection fraction (LVEF<35%), and a prolonged QRS complex (>120 ms), due to left or right bundle branch block (BBB),[1-4] and has been shown to reduce morbidity and mortality in a series of randomized trials.[5-9] In these patients, left ventricular (LV) function is impaired as a result of asynchronous contractions of the different segments within the left ventricle, as well as between the two ventricles. The primary aim of CRT is to restore the ven-

tricular contraction pattern, through synchronized biventricular pacing (BiV) with the use of an additional LV lead.[10]

On the other hand, in right ventricular (RV) apical pacing, which is the standard treatment for patients with severe bradyarrhythmias, the sequence of electrical activation resembles the activation pattern seen in LBBB.[11] This asynchronous electrical pattern is accompanied by abnormal mechanical interactions within the left ventricle and between the two ventricles, thus inducing dyssynchrony.[12-13] This is thought to be the reason why RV pacing has been shown, in some circumstances, to exacerbate symptoms of heart failure (HF) and increase hospital admissions.[14-15] In fact, randomized studies, comparing the effects of atrial vs. RV pacing, indicate that up to 40% of patients develop HF during VVIR pacing.[16-17]

The implementation of CRT, by means of BiV pacing, can reverse the aforementioned deleterious effects that originate from pacing-induced LV dyssynchrony, and recent data suggest that upgrading conventional RV pacing to biventricular pacing in patients with HF could improve electrical and mechanical LV synchrony and functional status.[18-19] The purpose of this study was to document the clinical response of chronically RV-paced patients who experienced new or worsening symptoms of HF and underwent upgrade of their device to a biventricular pacemaker and/or defibrillator. In every case, the enrolled subjects fulfilled the established indications for CRT.

Methods

Patients were eligible for this prospective nonrandomized single-center study if they had a previous pacemaker implantation and fulfilled the standard indications for cardiac resynchronization therapy, as defined by the ESC guidelines.[20] More specifically, the study population consisted of patients with either a VVIR or DDDR pacemaker and/or an implantable cardioverter-defibrillator (ICD), who had evidence of moderate to severe HF (NYHA class III-IV) despite maximum tolerated medical therapy, LV systolic dysfunction (LVEF<35%), and a prolonged QRS complex (>120 ms). Patients with both ischemic and nonischemic cardiomyopathy were studied. Those 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. During the study period, which lasted from the beginning of 2009 (February) until the end of 2010 (December), a total of 37 patients with prior pacemaker implantation, who were referred to our department either for battery depletion or for new or worsening HF symptoms, were found to be CRT candidates. Twenty two patients had DDDR/ICD-DR and fifteen had VVIR/ICD-VR systems (Table 1) with a mean RV pacing duration of 6.1 ± 5.7 years.

Table 1. Devices previously implanted.

	Pacemaker only	ICD
VVI/VVIR pacing	12	3
DDD/DDDR pacing	17	5

All of the enrolled subjects were predominantly RV paced (defined as ≥90% paced on the last two interrogations of the device before enrollment). RV apical pacing was confirmed by X-rays and electrocardiography. Pacing indications included complete heart block; atrial fibrillation with a slow ventricular response, necessitating continuous ventricular pacing; and symptomatic bradycardia in which there were sufficient intrinsic atrioventricular (AV) conduction disturbances to necessitate ≥90% ventricular pacing, even when the programmable AV delay was extended to the maximum allowable value.

The study protocol was submitted to and approved by the Bioethics Committee of the study site and all patients provided written informed consent to their enrolment in the study.

Before the implantation procedure, all patients were evaluated clinically. A detailed history was obtained and a physical examination was performed in order to assess HF symptoms, according to the NYHA classification, to confirm that CRT candidates had been on optimal medical therapy for six months before the upgrade procedure, and to identify possible serious comorbidities.

The clinical evaluation was repeated at the six-month follow-up visit and the symptoms (according to NYHA classification) were compared to those at baseline. Information regarding hospitalizations prior to the upgrade, in the last six months before implantation, and throughout the follow-up period, was also noted. In order to assess functional capacity objectively, all patients performed a six-minute walk test (6MWT), before and six months after implantation, in a suitable location, according to the guidelines of the American Thoracic Society.[21]

In addition, a 12-lead surface ECG in the supine position was obtained in all HF patients, to estimate whether electrical dyssynchrony was present. All EC-

Gs were recorded at a paper speed of 25 mm/s and the longest QRS complex from the precordial leads was used for QRS duration measurement. ECGs were also obtained immediately after implantation and during each subsequent visit.

CRT candidates underwent echocardiographic examination before implantation, with a commercially available ultrasonography system (Philips iE 33 along with S5-1 transducer), and all measurements were performed according to the guidelines of the American Society of Echocardiography. Of the conventional echo parameters, left ventricular end systolic volume (LVESV), end-diastolic volume (LVEDV), and ejection fraction (LVEF) were assessed using Simpson's equation from the apical 4-chamber and 2-chamber views. The aforementioned measurements were repeated during the six-month follow-up visit. Response to CRT was defined as a >15% decrease in LVESV.[22] Mechanical dyssynchrony was assessed through the use of opposing wall delay by tissue Doppler imaging, with a cut off value of 65 ms. However, its results were not used for patient selection, as such a course of action is not supported by the present guidelines. Patients also underwent echocardiography immediately after implantation, but this examination was performed solely to detect possible complications.

In selected cases, coronary angiography was performed to exclude coronary artery disease as the cause of worsening HF, and those who underwent revascularization were excluded from the study. In addition, subjects who did not already have an ICD underwent an electrophysiological study to assess whether a combined device (BiV-ICD) would be appropriate.

Transvenous biventricular pacemaker implantation was undertaken using standard techniques, under local anesthesia. All patients received an LV lead via the transvenous route through the coronary sinus delivery systems, after contrast venography had been performed to identify the appropriate lateral or anterolateral vein. Acceptable parameters were defined as a pacing threshold less than 3.5 V, with absence of phrenic nerve stimulation from the same site at 7.5 V.[23] The devices employed in this study were either biventricular pacemakers (CRT-P) or combined devices (CRT-D), depending on the history of ventricular arrhythmias or the result of the electrophysiological study. The devices were set to DDDR or VVIR mode and the AV delay was programmed at 150 ms, while the VV delay was set at 20 ms with LV stimulation occurring first. In the event that a patient deteriorated clinically after the initialization of CRT, optimization of the AV and VV delays under echocardiographic guidance was performed.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software for MS Windows. Quantitative values were expressed as means with standard deviations and were compared using the paired Student t-test. Differences were considered statistically significant if p-values were <0.05, while p-values between 0.05 and 0.15 indicated a statistical trend.

Results

The patient population consisted of 28 male and 9 female subjects with an average age of 71.4 ± 7.7 years. Patients had HF of either ischemic (n=23) or non-ischemic etiology (n=14), and their NYHA classification was either III or IV. QRS duration in these patients ranged from 140 ms to 210 ms and mean LVEF was 26.3 ± 5.4%). All of them were in paced rhythm and under optimal medical therapy (Table 2). Of the aforementioned population, LV lead placement was unsuccessful in 3 patients (8.3%), and those were not included in the presented analysis.

Table 2. Baseline characteristics of the study population.

Demographic and clinical characteristics		Medical therapy	
Age (y)	71.4 ± 7.7	Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	36 (97.3%)
Male/female (n)	26/11	Beta-blockers	34 (91.9%)
Ischemic/non-ischemic (n)	23/14	Aldosterone antagonists	25 (67.5%)
NYHA (Class)	III (28) - IV (9)	Loop diuretics	32 (86.5%)
QRS duration (ms)	157.3 ± 17.8		
LVEF (%)	26.3 ± 5.4		

NYHA – New York Heart Association; LVEF – left ventricular ejection fraction.

As expected, an overall reduction by 28 ms (from 157.3 ± 17.8 ms to 129.3 ± 9.5 ms, p<0.001) was observed in the duration of the QRS complex in the study population, between baseline and six-month assessment. A substantial clinical benefit was derived from the upgrade of the device. Twenty-nine of the patients (85.3%) experienced a noteworthy improvement in symptoms, indicated by a reduction in NYHA classification by approximately one grade. More specifically, mean NYHA classification in the study subjects was reduced from 3.3 ± 0.6 to 2.5 ± 0.9 (p<0.001). Functional capacity also increased considerably, as evidenced by the increase in the distance covered during the 6MWT, from 246 ± 105 m to 321 ± 101 m (p<0.001), between the first evaluation and the last follow-up visit. Subjects also experienced a benefit in terms of hospitalizations, as the number of hospital admissions diminished from 1.4 ± 1 to 0.7 ± 0.8 (p<0.001), comparing the six-month periods before and after the CRT upgrade (Table 3).

As far as the echocardiographic measures are concerned, systolic function was enhanced, as there was a noteworthy increase in LVEF during the study period, from 26.3 ± 5.4% to 31.4 ± 6.7% (p<0.001). This was accompanied by a significant reduction in LVESV, from 134.3 ± 46 mL to 111.9 ± 41.1 mL (p<0.001). According to the changes in LVESV, 27 patients were classified as responders (79.4%).

Discussion

In the present study, we observed that biventricular pacing through the implantation of a transvenous LV lead in previously RV-paced patients offers a substantial benefit in terms of symptoms, functional capacity and rate of hospitalizations, which is accompanied by an improvement in echocardiographic parameters and a decrease in QRS duration. The results presented in this study are, in general, consistent with the literature, and suggest that it is possible to partially reverse the deleterious effect of chronic RV pacing.

In most studies, the benefits of CRT have been demonstrated in patients with dyssynchrony due to an "intrinsic" LBBB, while patients with HF and previous RV-pacing systems were excluded from major clinical trials of CRT. In the current study, beneficial treatment effects of BiV pacing were shown in patients with RV-pacing–induced dyssynchrony (paced LBBB). Patients with HF and an RV pacemaker often fulfill the current criteria for CRT, and have an LBBB pattern on the electrocardiograph when paced. These patients may have significant interventricular dyssynchrony,[24] although the severity and frequency of these abnormalities in this group remain poorly explored.

A number of studies have reported on the effects of upgrading from RV pacing to biventricular pacing in either the acute setting or in the short term. Early reports examining the feasibility of adapting chronic RV pacemaker systems to provide biventricular stimulation showed improvements in quality of life in patients with HF, but without thoroughly assessing the echocardiographic response to resynchronization therapy.[17,25] Similar improvement in symptoms, functional capacity and quality of life emerged from additional crossover observational and retrospective studies.[12,18,26-28] Other reports examining the impact of CRT upgrade on the acute echocardiographic and hemodynamic effects of biventricular pacing indicated an acute increase in EF and a reduction in intraventricular mechanical delay.[19,29-30]

Several of these studies[12,19,29,31] found overall similar improvements induced by CRT in patients having a primary implantation as compared to patients receiving an upgrade procedure after chronic RV pacing, while Nägele et al extended these findings to the central hemodynamic response and prognostic data.[32] More specifically, while a number of reports indicate that implantation success and clinical response to CRT were comparable for patients un-

Table 3. Results.

Parameter	Before upgrade	After upgrade	p
QRS Duration (ms)	157.3 ± 17.8	129.3 ± 9.5	<0.001
NYHA Classification (grade)	3.3 ± 0.6	2.5 ± 0.9	<0.001
Six minute walk test (m)	246 ± 105	321 ± 101	<0.001
Rate of hospitalizations (per 6 months)	1.4 ± 1	0.7 ± 0.8	<0.001
LVEF (%)	26.3 ± 5.4	31.4 ± 6.7	<0.001
LVESV (ml)	134.3 ± 4	111.9 ± 41.1	<0.001

NYHA – New York Heart Association; LVEF – left ventricular ejection fraction; LVESV – left ventricular end-systolic volume.

dergoing *de novo* versus upgrade procedures,[18,29,33] in Nägele's study there was no difference in the hard endpoints of overall prognosis or the cardiac event rate between patients with primary CRT implants and upgrade patients.[32] Foley et al went a step further, showing that in patients with HF who are chronically RV paced, upgrading to CRT is associated with long-term mortality and morbidity similar to those of patients undergoing *de novo* CRT. In addition to the clinical benefit, they observed no difference between these groups in terms of the composite endpoints of death or unplanned hospitalization for major cardiovascular events, death from any cause or unplanned hospitalization for HF, death from any cause or cardiovascular death, over a median follow-up period of 2.1 years.[34]

Foley et al also found evidence that upgrading to CRT was associated with reverse LV remodeling. These finding were later verified in two more recent studies, while evidence of a regression in LVESV was also present in our report. Vatankulu et al showed that upgrading RV pacing to a biventricular system resulted in significant remodeling of the left ventricle in medium-term follow up, and Fröhlich et al added that the improvement in LV reverse remodeling and the response to CRT were similar in the *de novo* CRT and CRT upgrade groups.[35-36] In the former report, a greater decrease in LV cavity size was found in patients with normal left atrial pressures (nonrestrictive filling pattern) compared with those with restrictive filling, while the increase in LV systolic function was correlated with the decrease in intraventricular dyssynchrony. The question of dyssynchrony in RV-paced subjects who undergo CRT upgrade had already been studied by Witte et al, who highlighted the fact that the frequency, severity and pattern of ventricular dyssynchrony in patients with congestive HF and RV pacing was not different from that observed in patients with intrinsic LBBB. Further, the impact of CRT on these abnormalities was found not to be different in those with RV-pacing–induced LBBB as compared with those with an intrinsic LBBB.[12]

The mechanisms of the observed benefit are believed to be similar to those involved in *de novo* resynchronization therapy. The main mechanisms seem to be the increase in AV synchrony, the decrease in the degree of mitral regurgitation, and the correction of inter- and intraventricular dyssynchrony. Both earlier reports and the findings of Nägele et al imply that BiV synchronizes mechanical activation in different myocardial regions in patients upgraded from RV pacing and improves their hemodynamics, especially through the augmentation of the mean arterial pressure on exercise.[32]

Important clinical issues related to upgrading pre-existing non-BiV devices to BiV, which concern the complexity and possible technical difficulties during implantation, have not been assessed prospectively. Problems such as more difficult access to the coronary sinus from the right side, passage of pre-existing chronically implanted leads that may have grown into the venous wall, or may obstruct the subclavian or caval veins, or may be attached to the tricuspid valve, prohibiting cannulation of the coronary sinus ostium, should be anticipated in upgrade procedures.[37] A study in 56 patients with CRT upgrade procedures reported implantation success in only 82% of attempts,[27] while *de novo* implantation is generally successful in >90-95% of patients.[2-3,38-39] In contrast, Duray et al demonstrated that CRT upgrade can be achieved with similar success as in *de novo* implantations, while Bogale et al reported no difference in the frequency of periprocedural complications.[31,40]

Despite the numerous small studies that have previously demonstrated favorable short- and long-term outcomes in patients undergoing CRT as an upgrade to a standard RV pacemaker, the practice of upgrading pacing systems in possible CRT candidates is not yet widespread. This option is mentioned in guidelines, albeit with a class IIa (level of evidence: C) recommendation, mainly due to the fact that the efficacy of CRT in this patient group has not been established with data from large trials.[20,41] The recent Resynchronization–Defibrillation for Ambulatory Heart Failure Trial included a small number (135/1798) of previously paced patients, but subgroup analysis did not reveal a clinical benefit of upgrading to CRT.[42] However, this trial focused on mild to moderate HF, while our sample consisted of patients with moderate to severe HF.

Limitations

In this study, the patient sample was rather small and further division of the patents into responders and non-responders was not deemed appropriate. Thus, caution is warranted before any attempt to generalize the results is made. Also, the study was observational and non-randomized, and there was not a direct comparison with *de novo* BiV implantations.

Conclusion

Upgrading to cardiac resynchronization therapy in chronically RV-paced patients offers substantial clinical benefits in terms of symptoms, functional capacity, and rate of hospital admissions, which are accompanied by an improvement in systolic function. Therefore, careful reevaluation is warranted of predominately RV-paced patients who have either battery depletion or new symptoms related to heart failure, and a possible upgrade to CRT would be a reasonable strategy.

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