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Chapter 22

Effects of interruption of long-term cardiac resynchronization therapy on left ventricular function and dyssynchrony

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ABSTRACT

Background: Interruption of short-term cardiac resynchronization therapy (CRT) has been shown to acutely worsen left ventricular (LV) function, mitral regurgitation, and LV dyssynchrony. The present study aims to assess whether LV reverse remodeling influences interruption of CRT, and, more practically, whether long-term continuous pacing is necessary in patients with reverse LV remodeling.

Methods: A total of 135 recipients of CRT were selected after showing LV reverse remodeling defined as a decrease in LV end-systolic volume $\geq 15\%$ after 6 months of CRT ("responders"). Echocardiography was performed at baseline and after 6 months with intermittent CRT on and off. LV dyssynchrony was determined using tissue Doppler imaging.

Results: During interruption of CRT, an acute deterioration in LV function, mitral regurgitation, and LV desynchronization were noted in responder patients. Of note, worsening of these echocardiographic measurements was observed, but they did not return to baseline values. For comparison, 100 nonresponder patients (without LV reverse remodeling) showed no significant echocardiographic changes during interruption.

Conclusions: Despite the presence of LV reverse remodeling, interruption of CRT resulted in worsening of LV function and desynchronization. Therefore, continuous long-term pacing is warranted to maintain the beneficial effects

INTRODUCTION

Cardiac resynchronization therapy (CRT) has become an established therapy in patients with advanced drug-refractory heart failure. Several studies have demonstrated acute hemodynamic improvement, long-term clinical and functional improvement, and reduced mortality and hospitalizations after CRT.¹⁻⁴ These benefits are attributed to a more synchronous contraction, augmented left ventricular (LV) systolic function, and consequently reverse LV remodeling.⁵ The question has been raised whether continued biventricular pacing is needed when LV function has improved and reverse LV remodeling has occurred after 6 months of CRT. It is currently unknown if interruption of long-term CRT would acutely worsen dyssynchrony in a reverse remodeled LV, and whether LV function would acutely deteriorate. Recent data in a small patient group with significant mitral regurgitation showed an immediate reduction in regurgitation after CRT initiation, followed by acute worsening of regurgitation during interruption of long-term CRT.⁶ The effects of interruption of CRT after 6 months pacing will be evaluated in a large group of responders to CRT (defined as significant reverse LV remodeling at 6 months follow-up). For comparison, the effects of interruption of CRT in nonresponders will also be evaluated.

METHODS

Patient population and protocol

A total of 250 consecutive patients received a CRT device according to the current guidelines: advanced heart failure (New York Heart Association [NYHA] class III or IV), depressed LV ejection fraction (<35%), and wide QRS complex (>120 ms).⁷ Clinical status was assessed at baseline and after 6 months of CRT, including assessment of NYHA class, quality-of-life score (using the Minnesota Living with Heart Failure questionnaire)⁸ and evaluation of exercise capacity using the 6-minute walking test.⁹ The echocardiographic analysis included evaluation at baseline and at 6-months follow-up. After data acquisition at 6-months follow-up, CRT was interrupted to perform echocardiography during intrinsic conduction or in right ventricular pacing in patients without intrinsic conduction; 135 (54%) patients were classified as echocardiographic responders after showing a reduction in LV end-systolic volume of $\geq 15\%$ after 6 months of CRT.^{10,11} These 135 patients formed the main focus of the present study, but the echocardiographic effects of CRT interruption in nonresponders were also evaluated.

Echocardiographic evaluation

All echocardiographic studies were performed the day before device implantation and at 6-months follow-up with CRT on and off. The CRT device was turned off for 5 minutes before the “off” acquisition started.⁶ Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine-loop format for off-line analysis (EchoPac 6.0.1, GE Medical Systems, Horten, Norway). LV volumes were derived and LV ejection fraction was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson’s technique.¹² The severity of mitral regurgitation was graded semi quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 3-point scale: mild (jet area/left atrial [LA] area <20%), moderate (jet area/LA area 20% to 45%), and severe (jet area/LA area >45%).¹³

In addition, the maximal rate of LV systolic pressure increase (LV dP/dt) was estimated from the steepest rising segment on the continuous wave Doppler regurgitant jet.¹⁴ Tissue Doppler imaging was performed using the apical 4- and 2-chamber views as previously described.¹¹ Views were optimized for pulse repetition frequency, color saturation, sector size, and depth, allowing the highest possible frame rate. At least 3 consecutive beats were stored and images were analyzed off-line (EchoPac 6.0.1). The sample volumes were placed in the basal portions of the septum, lateral, anterior, and inferior walls; per region, the time interval between the onset of QRS and the peak systolic velocity was derived. LV dyssynchrony was calculated as the maximum delay between peak systolic velocities in the 4 walls (most frequently observed between the septum and the lateral wall).

Device implantation

Device implantation started with obtaining a coronary sinus venogram with a balloon catheter, followed by the insertion of the LV pacing lead. An 8Fr guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota, or Attain-SD4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or posterolateral vein.¹⁵ The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual chamber biventricular implantable cardioverter defibrillator (ICD) (Contak Renewal II or H195, Guidant Corporation, St. Paul, Minnesota, or Insync III or Insync Sentry, Medtronic Inc., Minneapolis, Minnesota).

Statistical analysis

Continuous variables are expressed as mean±SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between responders and nonresponders were analyzed using unpaired Student's t tests (continuous variables) and chi-square or Fisher's exact tests (dichotomous variables) as appropriate. The paired Student's t test was used to compare continuous data within the sub-groups during follow-up. For all tests, a p-value <0.05 was considered statistically significant.

RESULTS

Patients

Baseline characteristics of the 135 echocardiographic responders (102 men, mean age 67±10 years) included in this study are summarized in Table 1. Patients had severely depressed LV function, with a mean LV ejection fraction of 26±7%. Substantial LV dyssynchrony was present, as indicated by a mean delay of 96±37 ms. Device implantation was successful in all patients and no procedure related complication was reported.

Table 1. Baseline characteristics in responders and nonresponders to CRT

Variable	Responders (n = 135)	Nonresponders (n = 100)	p-value
Age (years)	67 ± 10	64 ± 11	0.011
Men / Women	102 / 33	82 / 18	0.2
Ischemic cardiomyopathy	70 (52%)	73 (73%)	<0.001
QRS duration (ms)	160 ± 32	143 ± 31	<0.001
NYHA class II / III / IV	14 / 117 / 4	9 / 82 / 9	0.1
Quality-of-life score	34 ± 17	38 ± 21	0.1
6-minute walking distance (m)	300 ± 127	326 ± 93	0.1
LV ejection fraction (%)	26 ± 7	27 ± 9	0.8
LV end-diastolic volume (ml)	216 ± 63	219 ± 80	0.7
LV end-systolic volume (ml)	160 ± 53	163 ± 72	0.7
Mitral regurgitation (moderate-to-severe)	25 (19%)	16 (16%)	0.2
LV dyssynchrony (ms)	96 ± 37	52 ± 38	<0.001

Changes at 6 months follow-up after CRT

After 6 months of CRT, 123 patients (91%) showed an improvement of ≥ 1 NYHA functional class (105 patients showed an improvement of 1 NYHA class, 18 patients showed an improvement of 2 NYHA classes vs. baseline, $p < 0.001$). The quality-of-life score improved from 34 ± 17 to 19 ± 18 ($p < 0.001$), and exercise capacity improved as indicated by an increase in 6-minute walking distance from 298 ± 126 m to 420 ± 170 m ($p < 0.001$). In addition, LV ejection fraction improved from $26 \pm 7\%$ to $38 \pm 9\%$ ($p < 0.001$), with a reduction in LV end-diastolic (216 ± 63 ml to 165 ± 56 ml, $p < 0.001$) and LV end-systolic volume (160 ± 53 ml to 104 ± 44 ml, $p < 0.001$). Furthermore, severity in mitral regurgitation decreased as demonstrated by a reduction in jet area/LA area from $16 \pm 16\%$ to $8 \pm 10\%$ ($p < 0.001$) as well as an increase in LV dP/dt from 708 ± 304 mm Hg/s to $1,136 \pm 429$ mm Hg/s ($p < 0.001$). Also, 6 months of CRT resulted in a significant decrease in LV dyssynchrony from 96 ± 37 ms to 32 ± 29 ms ($p < 0.001$).

Effects of interruption of CRT

As shown in Figure 1, interruption of CRT resulted in an acute deterioration of all echocardiographic measurements; LV end-systolic volume increased to 116 ± 47 ml and LV ejection fraction decreased to $32 \pm 9\%$ as compared with 6 months follow-up (both $p < 0.001$). In addition, acute worsening of severity in mitral regurgitation was noted (jet area/LA area increased from $8 \pm 10\%$ to $12 \pm 14\%$ and LV dP/dt from $1,136 \pm 429$ mm Hg/s to 757 ± 259 mm Hg/s, both $p < 0.001$). Also, the extent of LV dyssynchrony acutely increased to 60 ± 37 ms ($p < 0.001$). Of interest, although worsening of these features was observed, the different measurements did not return completely to baseline values (Figure 1).

Of note, 15 patients died within the 6-month follow-up and 100 patients showed a reduction in LV end-systolic volume of $< 15\%$, and were thus classified as nonresponders. Baseline characteristics between responders and nonresponders were comparable except that responders had higher age, longer QRS duration, more extensive LV dyssynchrony, and less often ischemic cardiomyopathy (Table 1). Interruption of CRT in nonresponders did not cause immediate significant deterioration of LV function, LV dyssynchrony, nor severity in mitral regurgitation (Table 2).

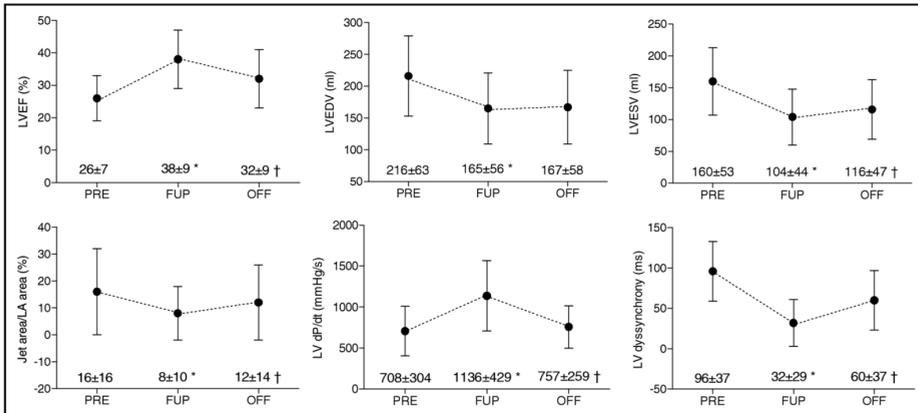


Figure 1. Echocardiographic measurements at baseline (PRE), 6-months follow-up (FUP), and during interruption of CRT (OFF) in 135 CRT responders. *PRE vs. FUP, $p < 0.001$; †FUP vs. OFF, $p < 0.001$.

LVEDV = LV end-diastolic volume; LVEF = LV ejection fraction; LVESV = LV end-systolic volume.

Table 2. Echocardiographic measurements in 100 nonresponders to CRT at 6 months follow-up and during interruption of pacing

Variable	Follow-up	Interruption of Pacing	p-value
LV ejection fraction (%)	27 ± 8	27 ± 8	0.5
LV end-diastolic volume (ml)	223 ± 79	225 ± 79	0.1
LV end-systolic volume (ml)	161 ± 69	167 ± 67	0.1
Jet area/LA area (%)	14 ± 16	14 ± 16	0.5
LV dP/dt (mmHg/s)	733 ± 289	644 ± 202	<0.001
LV dyssynchrony (ms)	45 ± 35	50 ± 37	0.1

DISCUSSION

The results of the present study can be summarized as follows: (1) interruption of long-term CRT resulted in acute deterioration of LV function, mitral regurgitation, and LV desynchronization in CRT responder patients; (2) although worsening of these echocardiographic features was observed, the values did not return to baseline; and (3) nonresponder patients did not show significant echocardiographic changes during interruption.

CRT studies in the acute setting have demonstrated that CRT abruptly improves hemodynamics and LV function.^{1,16} Importantly, this effect disappears immediately when the device is turned off again.¹⁷ However, only few small studies report on the effects of interruption of long-term CRT and its effect on LV function, severity of mitral regurgitation, and LV dyssynchrony. Yu et al⁵ performed serial echocardiographic examinations in 25 recipients of CRT. After 3 months of continuous CRT, interruption caused immediate worsening of LV function (LV ejection fraction decreased from $40.0 \pm 14.7\%$ to $33.6 \pm 13.2\%$, $p = 0.01$); however, no significant changes in LV volumes were observed. In addition, worsening of mitral regurgitation was noticed as demonstrated by an increase in jet area/LA area (from $18 \pm 15\%$ to $28 \pm 16\%$) and LV dP/dt (from 912 ± 229 mm Hg/s to 676 ± 152 mm Hg/s, both $p < 0.05$). Regarding LV dyssynchrony, Yu et al used tissue Doppler imaging to calculate the SD of the time delays of 12 LV segments. The authors demonstrated that after 3 months of pacing the SD of the time delays was significantly shorter as compared with baseline (37.7 ± 10.9 ms vs. 29.3 ± 8.3 ms, $p < 0.05$). When pacing was stopped, the SD of the time delays increased immediately to 41.1 ± 11.8 ms vs. 3 months ($p < 0.01$). Another small study by Brandt et al¹⁸ focused on the hemodynamic effects of temporary interruption of CRT after a mean of 427 days. Withdrawal of CRT resulted in a decline of LV dP/dt (from 711 to 442 mm Hg/s, $p < 0.001$) and an increase in mitral regurgitation (jet area/LA area 13.8% to 20.3%, $p = 0.004$). In addition, an acute deterioration of LV function and LV volumes was noted. Lastly, Ypenburg et al⁶ evaluated a selected group of 25 patients who demonstrated an acute reduction in mitral regurgitation after CRT initiation (jet area/LA area from $40 \pm 13\%$ to $25 \pm 11\%$, $p < 0.001$). Interruption of CRT after 6 months resulted in acute worsening of mitral regurgitation as well as LV function. Importantly, dyssynchrony involving the papillary muscles showed similar deterioration during CRT withdrawal. The present study is the first to evaluate the effect of CRT withdrawal in a reverse remodeled LV in a large group of patients. The current data demonstrate that withdrawal of CRT, even after long-term CRT with clear evidence of LV reverse remodeling, resulted in acute deterioration of LV function and mitral regurgitation. Importantly, this deterioration is accompanied by a more dyssynchronous contraction as demonstrated by an acute increase in LV dyssynchrony. This implies that the beneficial effect of LV reverse remodeling is pacing dependent and that continuous pacing is warranted. However, the measurements did not return to baseline levels, probably as a result of LV remodeling. Preliminary data suggested that long-term withdrawal of CRT may result in return to baseline values.⁵ Furthermore, the present study evaluated the

interruption effect after 6 months of CRT; it is currently unknown if this deterioration would be less during the off state after, say, 12 months or even disappear at some time. Further study is warranted to evaluate the precise effects of CRT over time.

The current data are supported by the findings in the nonresponder patients, who did not show echocardiographic improvement after CRT and consequently did not show deterioration during withdrawal of CRT.

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