Is “Hyper Response” to Cardiac Resynchronization Therapy in Patients with Nonischemic Cardiomyopathy a Recovery, a Remission, or a Control?

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Background and Objectives: Some patients treated by cardiac resynchronization therapy (CRT) recover “normal” left ventricular (LV) function and functional status. However, whether this “normalization” persists or reverts over time remains unknown. The aim of the present study was to evaluate the long-term outcomes of LV function in patients hyper responder to CRT.

Methods: Eleven consecutive patients with nonischemic dilated cardiomyopathy, sinus rhythm, left bundle branch block (LBBB), New York Heart Association (NYHA) class III or IV, and optimal pharmacological treatment were hyper responder as they fulfilled concurrently the two following criteria: functional recovery (NYHA class I or II) and normalization of LV ejection fraction (LVEF).

Results: After a mean follow-up of 65 ± 30 months between CRT implantation and last evaluation LVEF improved from 26 ± 9 to $59 \pm 6\%$ ($P < 0.0001$). One patient died from pulmonary embolism 31 months after implantation. Three patients exhibited $\text{LVEF} \leq 50\%$ at their last follow-up visit (two at 40% and one at 45%). In eight patients, brief cessation of pacing was feasible (three were pacemaker-dependent). Mean QRS duration decreased from 181 ± 23 ms to 143 ± 22 ms ($P = 0.006$). In one patient, pacing was interrupted for 2 years and LVEF decreased markedly (from 65% to 31%) but returned to normal after a few months when pacing was resumed.

Conclusion: In hyper responder patients, “normalization” of LV function after CRT persists as long as pacing is maintained with an excellent survival.

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Cardiac resynchronization therapy (CRT) is a recommended therapy in patients with sinus rhythm, long QRS duration, and severe congestive chronic heart failure (CHF) in spite of maximal tolerated pharmacological treatment.^{1,2} However, it has been reported, almost since the beginning of CRT that one-third of the patients who satisfied the above-mentioned criteria were not improved.³ This observation gave rise to the concept of “nonresponders” to CRT. Surprisingly, the opposite of the concept of “nonresponders,” that is, patients with an impressive improvement after CRT has not been evaluated until recently.^{4,5} These “hyper responders” are so dramatically improved that they are considered to have recovered a “normal” heart. They are recruited exclusively in patients with

nonischemic dilated cardiomyopathy (NIDCM) and their proportion within this cohort is significant, close to 20%.⁶ A previous publication failed to identify a unique factor that could really discriminate before implantation “hyper responders” from others. However, although values are not statistically different, there is a trend for “hyper responders” to have a less subjective and objective deterioration of baseline parameters.⁷ We have already reported a middle-term evolution of these patients, but their long-term evolution after recovery remains unknown. Aim of the present study is to recognize if (1) this “normalization” is just transient with a subsequent progressive deterioration or, if it is persistent over years (2) improvement is directly linked to CRT.

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METHODS

Patient Selection

This prospective, observational study was conducted among patients consecutively admitted in our department from 1996 to 2006 in sinus rhythm with a permanent left bundle branch block (LBBB) (QRS duration ≥ 140 ms) for evaluation and treatment of NIDCM with low left ventricular (LV) ejection fraction (EF $\leq 35\%$ and LV end-diastolic diameter ≥ 60 mm). All patients had severe CHF (New York Heart Association [NYHA] class III or IV) lasting for more than 6 months in spite of a maximal tolerated pharmacological treatment in accordance with the guidelines in use at the time of their admission and implanted with a CRT device. Intra-LV dyssynchrony was assessed by echocardiography but the final decision to implant or not a CRT pacing system was not based exclusively on the results of this examination.⁸ Patients were classified in the NIDCM group on the results of a recent coronary angiography.

Patients with a potential reversible cause of NIDCM were excluded, particularly those with chronic alcoholic consumption (>80 g/day) or long-lasting tachycardia including atrial fibrillation. Patients previously implanted with a right ventricular pacing system even if they fulfilled the inclusion criteria and were "hyper responder" to CRT were also excluded from the present study.

Patients were classified "hyper responders" when they satisfied simultaneously at any time during follow-up the two following criteria: NYHA class I or II and normal left ventricular ejection fraction (LVEF) measured by radionuclide ventriculography. In our laboratory, the normal value of LVEF is $55 \pm 3\%$. A two standard deviation is 6% consequently an LVEF $\geq 50\%$ is considered normal.

Implantation Procedure

The transvenous approach for CRT used in our center has been previously described in detail.^{9,10} The atrioventricular delay was individually programmed before discharge using previously published echocardiographic criteria.¹¹ No interventricular (VV) interval optimization was performed. Our implantation success rate of LV leads was calculated at 95%,¹² in accordance with published data.¹³

Patient Follow-Up Procedure

All consecutive patients who fulfilled the above-mentioned criteria were prospectively followed at 1, 6, and 12 months after implantation of a CRT device and every year thereafter until death or closure of the present study. Only patients followed for more than 2 years after implantation were included in the present study group.

Data Collection

Baseline characteristics were collected within 2 weeks before implantation of the CRT device.⁶ The LVEF values reported in the present study were those measured by gated equilibrium radionuclide ventriculography.

All parameters collected at baseline were reassessed at each follow-up visit in addition to the appropriate functioning of the device. Patients were advised to take precisely their pharmacological treatment and to modify this treatment only after advice of a physician of the cardiology department.

All "hyper responder" patients were reviewed during the second term of 2008 and asked to accept to have their pacemaker turned "off" (VVI 30/min, a pacemaker that stimulates and senses the ventricle at 30/min.) for a few minutes to allow analysis of the spontaneous QRS duration and morphology. The first "hyper responder" patient implanted in our center at the beginning of our experience (March 1996) had a different programming reported in detail in the results section.

It should be stressed that implantation procedures and follow-up were achieved by different physicians in and out the department of cardiology and that they were not systematically aware of the aim of the present study.

Objectives of the Study

They are reported in the introduction. Our evaluation was based on values of LVEF an objective parameter recorded by physicians blinded to the aim of the study.

Statistical Analysis

Values were expressed as mean $\pm$ standard deviation. Comparison of parameters between baseline and the follow-up visits was made using Student's paired *t*-test. Comparison of LVEF between

follow-up visits was performed using a one-way analysis of variance. An unpaired *t*-test was used for comparison between patients with and without normalization of LVEF.

Differences were considered significant when the *P* value was <0.05.

RESULTS

Study Population

It consisted of 11 "hyper responder" patients after implantation of the CRT (mean age at implantation: 71.4 ± 6 years, six males) recruited among the 84 patients successively implanted and followed for at least 24 months. Mean duration of heart failure symptoms before implantation was 40 ± 35 months and in spite of maximal tolerated pharmacological treatment, patients remained or evolved to severe heart failure (nine were in NYHA class III and two in class IV). Before implantation patients were treated by diuretics (seven patients) and angiotensin converting enzyme inhibitor (ACE) inhibitors (all patients), eight had beta-blockers (not tolerated in the three remaining patients) and two had spironolactone. Baseline characteristics of the study group are reported in Table 1. None had sinus node dysfunction.

Evolution of the Main Parameters during Follow-Up

Parameters recorded at baseline were also recorded during the last visit before closure of

Table 1. Baseline Characteristics before CRT Implantation in Hyper Responder Patients Group (N = 11)

	N = 11
Mean age (years)	71.4 ± 6
Men (%)	45.5
Heart failure duration (months)	40 ± 35
Left ventricular ejection fraction (%)	26 ± 9
Left ventricular diameter (mm)	73 ± 8
Peak oxygen consumption (mL/min per kg)	13.3 ± 4
6 minutes walked distance (m)	370 ± 116
Mean NYHA class	3.3 ± 0.5
QRS duration (ms)	172 ± 24
Mitral regurgitation	1.4 ± 1
Beta-blockers (%)	73
Angiotensin receptor antagonist or angiotensin converting inhibitor (%)	100
Diuretics (%)	64

Table 2. Characteristics of Patients at Baseline and at Last Follow-Up Visit in Hyper Responder Patients Group (Mean Duration Follow-Up: 65 ± 30 Months) (N = 11)

	Baseline	Last Follow-Up Visit
Left ventricular ejection fraction (%)	26 ± 9	59 ± 6
Left ventricular diameter (mm)	73 ± 8	55 ± 5
Peak oxygen consumption (mL/min per kg)	13.3 ± 4	18 ± 0.2
6 minutes walked distance (m)	370 ± 116	459 ± 67
Mean NYHA class	3.3 ± 0.5	1.4 ± 0.5
QRS duration (ms)	172 ± 24	145 ± 20
Mitral regurgitation	1.4 ± 1	0.2 ± 0.4

the study or before death and their mean values are reported in Table 2. The mean follow-up duration after implantation of the CRT device was 65 ± 30 months (from 31 to 136 months) and 50 ± 35 months (from 24 to 114 months) after the date when the patient was classified "hyper responder." During that period only one patient died from pulmonary embolism 31 months after implantation and while at the last follow-up visit (2 months before death) he remained "hyper responder." Importantly, we have not observed any patient qualified as hyper responders who died during the first 24 months after implantation.

Evolution of LVEF in the Study Group

LVEF improved from 26 ± 9 to $59 \pm 6\%$ ($P = 0.0001$) between baseline and last follow-up visit. Normalization of LVEF was observed after a relatively long period following implantation of CRT device: two patients within 1 month, two between 1 and 6 months, four between 6 and 12 months, two between 12 and 24 months, and more than 24 months in one case. The individual evolution of LVEF is reported in Figure 1. Only three patients had not an LVEF $\geq 50\%$ at their last follow-up visit (two were at 40% and one at 45%). For the group, the mean value of LVEF was maintained above 50% during the total period of follow-up without any trend to decrease (Fig. 2).

Figure 1. Individual evolution of left ventricular ejection fraction of the patients included in study group.

Evolution of QRS duration after Cessation of Pacing

In eight patients, brief cessation of pacing was feasible (three evolved to complete atrioventricular (AV) block and were pacemaker-dependent). Mean QRS duration decreased from 181 ± 23 ms to 143 ± 22 ms ($P = 0.006$). In the patient with a long-term cessation of pacing, spontaneous QRS duration regressed from 234 ms to 164 ms after CRT but increased to 170 ms 2 years after cessation of pacing.

Evolution of LVEF after Cessation of Pacing

Evolution of our first "hyper responder" patient after termination of pacing needs to be reported

in details. This patient had a "complete" recovery for several years and as there was no recommendation in the international guidelines to pace a patient with a normal ventricular function, she accepted to have the pacemaker turned "off." After 2 years without pacing, LVEF declined markedly (from 65% to 31%). Interestingly, LV end-diastolic dimensions also deteriorated from 46 mm to 62 mm. Although the patient remained asymptomatic, we considered that this progressive deterioration was significant enough and CRT was resumed. After 2 years, LV function gradually returned to normal (Fig. 3).

DISCUSSION

The main result of the present study is to establish that the outstanding evolution of "hyper responder" patients is maintained over several years.

Possible Evolutions after Recovery in Chronic Diseases

When a patient affected by a chronic disease such as heart failure, recovers a normal or near normal condition after a certain period of treatment, four evolutions are subsequently feasible: (1) treatment is interrupted and recovery is confirmed during long-term follow-up without relapse: the patient is cured; (2) treatment is interrupted after recovery but after some delay initial disease recurs

Figure 2. Global evolution of the left ventricular ejection fraction of the patients included in the study group.

Figure 3. Evolution of left ventricular ejection fraction and left end diastolic diameter in the first patient with a “complete recovery” after CRT observed in our department.

and the initial effective treatment is no longer or incompletely effective, recovery was just a remission (e.g., in cancers); (3) treatment is continued after recovery but patient progressively return to the initial status (e.g., in CHF^{14,15}) in that case recovery was just a temporary control; (4) treatment is continued after recovery, patient remains stable and treatment can be disrupted but after a certain delay the initial disease reappeared. To discriminate this latter evolution from remission, reinitiation of treatment is followed by a renewed recovery. In that case, recovery is under persistent control by treatment (e.g., in patients with AIDS).

Recovery in Patients with Severe Heart Failure

In patients with long-standing and severe signs of heart failure, recovery of normal or near normal cardiac function for a long period is an exceptional finding. In fact, this evolution has mainly been reported in patients with alcoholic addiction who have accepted to discontinue completely alcohol consumption or in patients after total control of permanent tachycardia.^{16–18} It has been reported some significant reverse remodeling after initiation of appropriate pharmacological treatment,^{19–21} but this remodeling is limited and this explanation is not appropriate in our series of patients “optimally” treated for several months or years with maintenance of the same treatment after implantation of the CRT.

Recovery in Patients with Severe Heart Failure after CRT

Complete recovery after CRT was initially reported in some cases.⁶ However, due to the lack of

long-term follow-up, it was impossible to classify this recovery as a cure, a remission, or a control by treatment. Results of the present study give some new information on the long-term evolution following recovery. Recently, a Danish study²² reported a 5-year follow-up of patients treated by CRT but not in “hyper responder” patients. Interestingly, in this series the “good” evolution was maintained over time.

Evolution When CRT Is Prolonged

In our group of highly selected patients, recovery is preserved after a mean follow-up of 5 years. It is obvious that there is no long-term significant deterioration of functional and objective status of patients following recovery. This observation excludes a potential advance of the disease after recovery namely progressive deterioration in spite of prolongation of treatment. However, this observation does not eliminate the possibility of complete cure as only a discontinuation of the effective treatment could give a response to this question.

Evolution When CRT Is Interrupted: Curing?

We have reported only one case of long-term interruption of pacing (2 years) and in that case there is almost a return to the pre-CRT parameters, although the patient had not already exhibited clinical signs of overt heart failure. Finally, it could be hypothesized, based on this demonstrative single patient, that “hyper responder” patients to CRT are not cured.

Evolution When CRT Is Continued: Remission?

It is not possible at present to completely exclude that the recovery observed in our patients was just a remission but considering the mean age of the patients and the usual prognosis of NYHA class III or IV patients after a 5-year follow-up with a dramatic reduction of LV systolic function this hypothesis seems unlikely.

Evolution When CRT Is Interrupted: Control?

This seems the most plausible hypothesis, although it depends on the observation of only one but demonstrative case. When CRT was initiated

in this NIDCM patient with wide LBBB, she was in NYHA class IV with an LVEF at 17%. She slowly recovered and after normalization of LV function for several years, pacing was interrupted and LV function decreased markedly therefore CRT was resumed and LV function returned to normal. This example demonstrates a relationship between evolution of LV function and CRT and supports the hypothesis of the persistence of recovery by a control of the underlying disease by pacing. More cases would be helpful to confirm this hypothesis.

What Is the Most Likely Mechanism?

Our theory has already been reported in details.^{4,6} In brief, we hypothesized that patients with persistent LBBB progressively deteriorate their LV function subsequently increasing QRS duration leading to a further decrease in LV function. This vicious circle stops in severe NIDCM through intimate mechanisms incompletely understood.^{19,23–27} The only mean to interrupt this vicious circle is to reverse LBBB by LV pacing. A strong argument in favor of this theory is the observation of a very significant decrease in spontaneous QRS duration, when pacing is resumed in our “hyper responder” patients.

Limitations

We have reported a limited number of patients but they were highly selected. Furthermore, “true hyper responder” patients to CRT although not uncommon⁶ are not so frequently found and their detection needs a careful long-term follow-up (this finding has only been reported 10 years after introduction of CRT). Long-term evolution is based on this limited group of patients but observations are very concordant among patients.

Conclusion

This study shows that “hyper responder” patients to CRT have an excellent long-term prognosis. Cessation of pacing results in reduction of LV function after several months. This observation seems to demonstrate that CRT does not cure these patients but allows a control of the underlying disease. Demonstration of a decrease in LBBB duration after recovery is a strong evidence to support the hypothesis of a vicious circle between LBBB and induction of NIDCM. Finally, the concept of

a new curative cause of NIDCM namely LBBB-induced cardiomyopathy seems promising.

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