SHOULD WE INCREASE BETABLOCKER AFTER CARDIAC RESYNCHRONIZATION THERAPY: THE RESULTS OF THE CARIBE-HF STUDY (CARDIAC RESYNCHRONIZATION IN COMBINATION WITH BETABLOCKER TREATMENT IN ADVANCED CHRONIC HEART FAILURE)

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Abstract

Cardiac resynchronization therapy (CRT), combined with optimal medical therapy (OMT), is an established treatment for patients with advanced chronic heart failure (ACHF). In ACHF, carvedilol at the dose used in clinical trials reduces morbidity and mortality. However, patients often cannot tolerate the drug at the targeted dosage. Aim of the CARIBE-HF prospective observational study was to investigate the role of CRT in the implementation of carvedilol therapy in patients with ACHF.

Methods: One hundred and 6 patients (aged 65±12 [mean±sd] years) with ACHF were enrolled and treated with OMT, in which carvedilol was titrated up to the maximal dose (phase 1). Subsequently, patients with left ventricular (LV) ejection fraction ≤ 35%, NYHA class III-IV and QRS interval ≥ 120 msec were assigned to CRT. Both CRT and NO-CRT patients underwent long-term follow-up till 7 years (1193,98±924 days), while efforts to up-titrate the carvedilol dose were continued during the second phase (471±310 days). Phase 1 was completed by 84 patients (79%), and 15 (18%) underwent CRT. The mean carvedilol dose in the CRT group was 19.0±17.8 mg, against 32.7±19.1 mg in the remaining 69 patients (p=0.018). At the end of phase 2, CRT patients presented a significantly greater variation of increasing in the carvedilol dose than NO-CRT patients (+20.0±19.8 mg vs –0.3±20.5 mg; p=0.015), a greater NYHA class reduction (-0.8±0.6 vs -0.2±0.7; p=0.011), and a greater increase in LV ejection fraction (+10.8±9 vs +3.1±6.1; p=0.018).

In conclusion, the data from the CARIBE study suggest that, in ACHF, CRT may be effective in enabling the target dose of carvedilol to be reached. The significant improvement seen in LV function was probably due to a synergistic effect of CRT and carvedilol. During the extended follow-up (mean 1193,98±924 days) the mean dosage of carvedilol in CRT group was significantly higher (p<0.02).

Key words: heart failure, beta-blockers, resynchronization therapy

Rezumat: Ar trebui majorată doza blocantelor după terapia de resincronizare cardiacă: rezultatele studiului CARIBE-HF

Terapia de resincronizare cardiacă (CRT), în asociere cu tratamentul optim medical (OMT), este recunoscută pentru pacienţii cu insuficienţă cardiacă cronică avansată (ACHF). În ACHF, carvedilolul la doza utilizată în studiile clinice reduce morbiditatea şi mortalitatea. Cu toate acestea, de multe ori pacienţii nu pot tolera beta-blocantul, la doza ţintă. Scopul studiului CARIBE-HF observaţional prospectiv a fost de a investiga rolul CRT în asocierea cu carvedilol la pacienţii cu ACHF.

Metodă: 106 pacienţi (cu vârsta de 65 ± 12 [media ± SD] de ani), cu ACHF au fost înrolaţi şi trataţi cu OMT, care a fost carvedilolul titrat la doza maximă (faza 1). Ulterior, pacienţii cu fracţia de ejecţie (VS) ≤35%, clasa NYHA III-IV şi QRS interval de ≥ 120 m/sec au fost supuşi CRT. Ambele grupe de pacienţi CRT şi CRT-NO au fost urmărite până

la 7 ani (1193,98 ± 924 zile), în timp ce titrarea în sus a dozei de carvedilol au continuat în faza a doua (471 ± 310 zile). La faza I au fost incluşi 84 de pacienţi (79%), iar 15 (18%) au fost supuse CRT. Doza medie carvedilol în grupul CRT a fost de 19.0 ± 17.8 mg, versus 32.7 ± 19.1 mg la alţi 69 de pacienţi (p = 0,018). La sfârşitul fazei 2, pacienţii cu CRT au prezentat o variaţie semnificativ mai mare de creştere a dozei de carvedilol decât pacienţii non-CRT (20.0 ± 19.8 mg vs -0.3 ± 20.5 mg, p = 0,015), o reducere a NYHA clasa (- 0,8 ± 0.6 vs -0.2 ± 0.7, p = 0,011), precum şi o creştere mai mare a fracţiei de ejecţie VS (+10,8 ± 9 vs 3.1 ± 6.1, p = 0,018).

În concluzie, studiul CARIBE sugerează că, în ACHF, CRT permite atingerea dozei ţintă de carvedilol. Îmbunătăţire semnificativă a funcţiei VS a fost, probabil, obţinută prin efectul sinergic al CRT şi carvedilolului. În timpul supravegherii (medie 1193,98 ± 924 zile) doza medie de carvedilol la pacienţii cu CRT a fost semnificativ mai mare (p <0,02).

Cuvinte-cheie: insuficienţă cardiacă, beta-blocante, terapia de resincronizare

Резюме: Нужно ли повышать дозу бета блокаторов после терапии сердечной ресинхронизации: результаты GARIBE-HF исследования

Сердечная ресинхронизация (CRT), в сочетании с оптимальной медикаментозной терапии (OMT), является апробированным лечения пациентов с выраженной хронической сердечной недостаточности (ACHF). При ACHF, карведилол, используемый в клинических исследованиях снижает смертность. Тем не менее, пациенты часто не переносят препарат в целевой дозы. Цель CARIB-HF исследования было изучение роли CRT в комбинации с карведилола у пациентов с ACHF.

Методы: 106 пациентов (в возрасте 65 ± 12 [средняя ± SD] лет) с ACHF были включены в исследовании с OMT, в котором карведилола был титрован до максимальной дозы (фаза 1). Впоследствии пациенты с фракцией выброса <35%, NYHA класс III-IV QRS и интервала >120 мс была проведена CRT. Обе группы больных с OMT и non-CRT больным наблюдались до 7 лет (1193,98 ± 924 дней), в то время предпринимались попытки повышать дозу карведилола в ходе второго этапа (471 ± 310 дней). Фаза 1 завершили 84 пациентов (79%), и 15 (18%) была CRT. Средние дозы карведилола в группе CRT был 19,0 ± 17,8 мг, против 32,7 ± 19,1 мг в оставшихся 69 пациентов (p = 0,018). В конце фазы 2, CRT пациентов представлено значительно большее изменение увеличения в дозе, чем карведилол NO-CRT пациентов (20,0 ± 19,8 мг против -0,3 ± 20,5 мг, p = 0,015), большая NYHA класс снижение (-0,8 ± 0,6 против -0,2 ± 0,7; p = 0,011) и большее увеличение фракции выброса левого желудочка (+10,8 ± 9 против 3,1 ± 6,1, p = 0,018).

В заключение, данные из CARIBE исследования свидетельствуют о том, что в ACHF, CRT может быть эффективной в обеспечении целевой дозы карведилола. Значительное улучшение функции ЛЖ, вероятно, из-за синергетического эффекта CRT и карведилола. Во время длительного наблюдения (средний 1193,98 ± 924 дней) средняя доза карведилола в CRT группе была значительно выше (p <0,02).

Ключевые слова: сердечная недостаточность, бета-блокаторы, синхронизация терапии

Introduction

Beta-blocker therapy in heart failure (HF) patients [1-7] produces an important hemodynamic and clinical improvement, reducing mortality and morbidity [5]. The benefits of beta-blockers are at least as great in patients with advanced HF as in those with less severe disease.

However, in clinical practice physicians treating patients with advanced chronic HF (ACHF) find it very difficult to reach the target dose of beta-blockers used in clinical trials and recommended by guidelines. Up-titration is most frequently limited by the worsening of clinical signs of HF, bradycardia and hypotension [8]. Cardiac resynchronization therapy (CRT) has been proposed for the treatment of patients with ACHF and mechanical dyssynchrony. Several clinical trials have shown the beneficial effect of CRT on clinical symptoms, exercise capacity and quality of life [9-17]. In the CARE-HF study [14], CRT reduces all-cause mortality and HF-related hospitalization. After successful implantation of the CRT device, a significant improvement in the hemodynamic profile is obtained [14]. Furthermore, neurohormonal activation is reduced, as shown by a fall in serum levels of BNP [14]. The subsequent improvement in HF symptoms, cardiac function and clinical stability may enable beta-blocker therapy to be started and up-titrated more successfully in patients with ACHF.

The aim of this prospective observational study was to investigate the role of CRT in the implementation of carvedilol therapy in patients with ACHF and electromechanical delay. In addition, the synergistic effect of CRT and carvedilol on left ventricular (LV) function was evaluated.

Methods

The CARIBE-HF (CArdiac Resynchronization In combination with BEtablocker treatment in advanced chronic Heart Failure) is a prospective observational

study, which, from March 13, 2002 to December 22, 2003, enrolled 106 patients admitted to hospital or examined in the outpatient clinic because of systolic HF with a LV ejection fraction (LVEF) ≤35% , and in NYHA functional class III or IV. Exclusion criteria were age < 18 year or life expectancy < 1 year for noncardiac conditions. The strategy adopted for the study is reported in figure 1.

In the first phase, optimal medical therapy (OMT) was implemented according to the recommendations of European Society of Cardiology guidelines, especially attempting to achieve maximal tolerated doses of beta-blockers [18]. At the end of this phase, CRT was proposed for patients still in NYHA functional class III or IV, with QRS interval ≥ 120 msec, and LVEF ≤35% (CRT group). Patients with a QRS interval of 120 to 149 msec were required to meet two of three additional criteria for dyssynchrony: an aortic preejection delay of more than 140 msec, an interventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral LV wall. Patients without CRT indications were assigned to the NO-CRT group. After assignment to one group or the other, patients entered the second phase of the study, during which all patients underwent a further attempt to start or increase carvedilol up to the maximum tolerated dose. At the end of each phase of the study, clinical and vital status, hospitalization and echocardiographic parameters of both groups were assessed and compared with the baseline.

During enrolment and follow-up, all patients were examined at the HF clinic; the echocardiographic evaluation was performed at baseline with Acuson Sequoia machine and during phase I and II with GE VIVID 5 machine by 2 expert cardiologists and reviewed by a third. During echocardiography, the index of myocardial performance or TEI-index of left and right ventricles were determined [19].

Patients with indication to CRT received a Medronic InSync or InSyn III Device, which provided atrial-based, biventricular stimulation by means of standard right atrial (Capsure Medtronic) and ventricular (Sprint Medtronic) leads. The LV lead (Attain Medtronic) was implanted to pace the lateral or postero-lateral LV wall transvenously.

An extended follow-up was carried out during december 2009.

Statistical analysis

Continuous variables were represented as average ± standard deviation, and categorical variables as absolute and relative frequency. Continuous distributions were compared by means of Student's T-test, and categorical variables by means of χ^2 or Fisher's Exact test, as appropriate. Comparisons

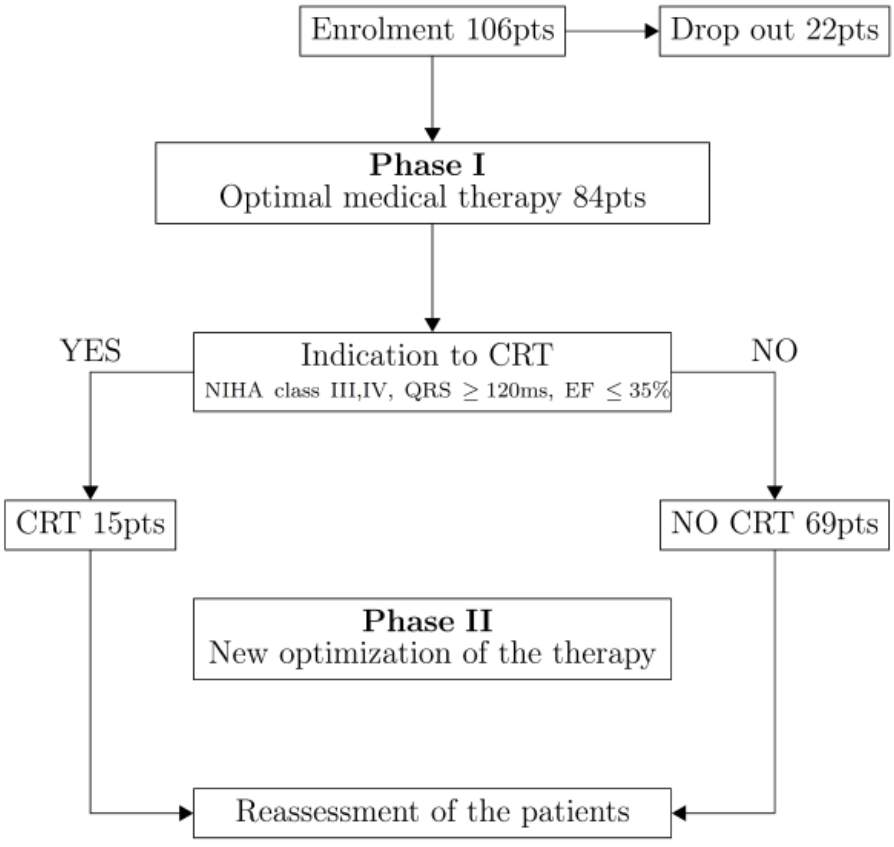

Figure 1. *Study design*

among baseline, phase 1 and phase 2 values were performed by using the GLM method for repeated measurements. A p value <0.05 was considered statistically significant. The SPSS 12.0 statistical software was used for all analyses.

Results

The mean age of the patients, was 65 ± 12 years, and most of whom were men (75%). The clinical characteristics of the population are reported in Table 1.

The first phase of the study lasted 163±111 days; at the end of this phase, a significant increase in the use of ACE-inhibitors or Angiotensin II Receptor Blockers, diuretics, spironolactone and carvedilol was recorded (Figure 2, p value < 0.001). The prevalence of carvedilol administration was slightly higher in comparison with ACE-inhibitors or Angiotensin II Receptor Blockers (92% vs 80%) and this could be explained by the intention-to treat strategy with betablockers of the study.

During the first phase, 22 patients (21%) dropped out of the study because of: death in 9 cases (6 due to HF, 2 non-cardiovascular cause, 1 unknown cause), coronary-artery bypass surgery in 2, heart transplantation in one, Pacemaker implantation in one, and low compliance in 9. The first phase of the study was completed by 84 patients (79%), 15 (18%) patients received a CRT (CRT group), and 69 (82%) patients received medical treatment only (NO-CRT group). All 84 patients completed the second phase

Table 1

Clinical characteristics of the patients enrolled in the study

Gender	*Males* *Female*	*80 pts* *26 pts*	*(75%)* *(25%)*
Age (years)	65 ± 12		(range 31-87)
HF etiology	Ischemic	60 pts	(56%)
	Idiopathic	39 pts	(37%)
	Hypertensive	3 pts	(3%)
	Other	4 pts	(4%)
NYHA class	III	82 pts	(77%)
	IV	24 pts	(23%)
Months since first HF diagnosis	46 ± 67		(range 0-359)
Hospitalizations number (H) in the last 12 months	No H	65 pts	(61%)
	1 H	30 pts	(28%)
	2 H	8 pts	(8%)
	3H	2 pts	(2%)
	4 H	1 pts	(1%)
Length of stay (days)	16 ± 11		(range 3 ± 60)
BBB	Left BBB	50 pts	(47 %)
	Right BBB	4 pts	(4%)
QRS duration (msec)	<120	34 pts	(32%)
	120-150	33 pts	(31%)
	>150	33 pts	(31%)
	PM	6 pts	(6%)
HR (bpm)	81 ± 15		
SBP (mm Hg)	113 ± 18		
DBP (mm Hg)	75 ± 11		
LV EDD (mm)	66 ± 8		
LV ESD (mm)	56 ± 10		
LV EDV (ml)	231 ± 62		
LV ESV (ml)	169 ± 58		
LV EF (%)	26 ± 7		
MR (degree)	2.0 ± 1.0		
LVMP index	0.95 ± 0.3		
RVMP index	0.7 ± 0.4		

(BBB – bundle branch block, PM –Pacemaker, HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, LV EDD – left ventricular end diastolic diameter, LV ESD – left ventricular end systolic diameter, LV EDV – left ventricular end diastolic volume, LV ESV – left ventricular end systolic volume, LV EF – left ventricular ejection fraction, MR – mitral regurgitation, LV MP – left ventricular myocardial performance, RVMP – right ventricular myocardial performance, pts - patients)

of the study (471±310 days). During this phase, 4 patients discontinued the carvedilol tratment, 1 in the CRT group because of symptomatic hypotension, and 3 patients in the NO-CRT group (1 for asthma and 2 for symptomatic hypotension).

At the end on the phase 1 clinical characteristics showed a lower systolic blood pressure and lower dose of carvedilol in the CRT group than in the NO-CRT group. Among 50 patients with left bundle branch block and QRS duration ≥ 120 msec at the end of phase 1, 35 (70%) were not considered for CRT implantion due to improvement of functional NYHA class (< II) in 20 and to a LVEF increase above 35% in 15. In the CRT group the cause of the carvedilol titration failure was blood pressure < 90 mm Hg in 7 (47%), clinical instability in 4 (26%), heart rate < 50 beat per minute in 1 (6%), and first degree AV block in 1 (6%). There is no difference between 2 groups at the end of the second phase (Table 2). Comparison of both groups at the end of the phase 1 and the phase 2 revealed that patients with indication to CRT therapy had a lower LVEF and a higher performance index that become almost equal at the end of the study (Table 3).

The dissynchrony data in the CRT group included: an aortic preejection delay 160±27 msec, an interventricular mechanical delay 50±23 msec, as well as delayed activation of the posterolateral LV wall was present.

At the end of the phase 2 (471±310 days)

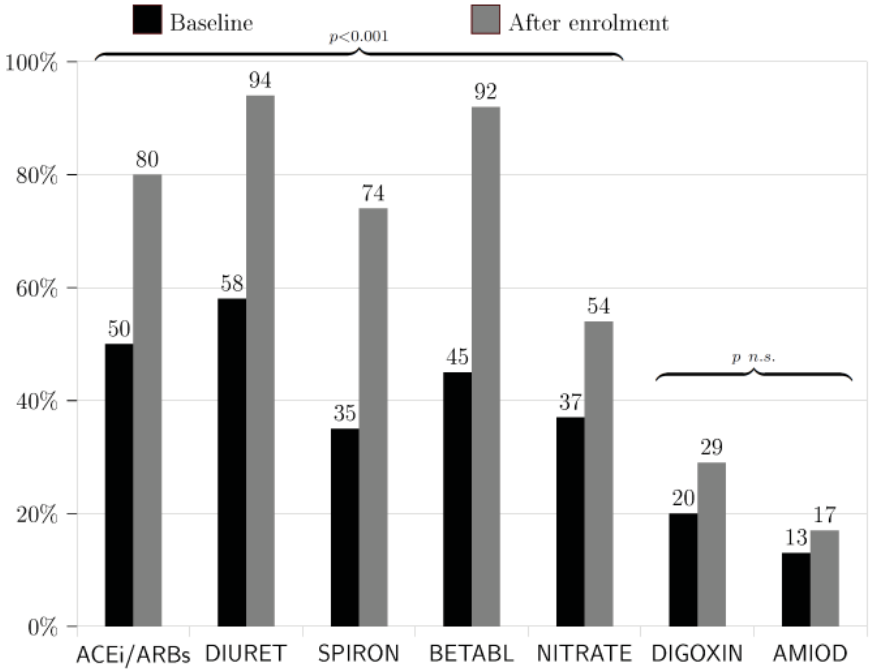

Figure 2. *Therapy of the study patients before and after enrolment. (ACE-i - angiotensin-converting enzyme inhibitors; ARBs - Angiotensin II receptor blockers, diuret – diuretics, spiron – Spironolattone, betabl – beta-blockers, amiod – Amiodarone)*

Table 2

Clinical characteristics of the patients in the CRT and NO-CRT groups

	Phase I			*Phase II*		
	CRT (15 pts)	**NO CRT** (69pts)	P value	**CRT** (15 pts)	**NO CRT** (69pts)	P value
NYHA I (%) II (%) III (%) IV (%)	0 53 47 0	20 60 20 0	0.045	40 47 13 0	33 52 15 0	n.s.
HF hospitalization in previous year (%)	33	22	n.s.	20	22	n.s.
HR (bpm)	74±11	66±15	n.s.	71±8	72±13	n.s.
SBP (mmHg)	106±12	124±20	<0.001	113±15	119±21	n.s.
DBP (mmHg)	69±7	75±11	0.017	70±9	72±11	n.s.
Carvedilol (%)	87%	91%	n.s.	80%	87%	n.s.
Carvedilol dose (mg)	19.0.±17.8	32.7±19.4	0.027	39.0±21.8	32.4±21.9	n.s.

significantly greater improvements were recorded in the CRT group than in the NO-CRT group regarding to both NYHA functional class (CRT -0.8±0.6 vs NO-CRT -0.2±0.7, p value 0.011) and LV EF (CRT +10.8±9.1 vs NO CRT +3.1±6.1, p value 0.018) (Figures 3a, 3b).

The dose of carvedilol did not differ significantly between the groups at the baseline and at the end of the second phase, while it was significantly higher in the NO-CRT group at the end of the first phase (p=0.027). In the CRT group the carvedilol dose was significantly higher after CRT than at the end of the first phase (39.0±21.8 vs 19.0±17.8 mg, p<0.0001), while no significant differences were found during the same period in the NO-CRT (Figure 4). During the extended follow-up (mean 1193,98±924 days) the mean carvedilol dosage was significantly higher in the CRT vs NO-CRT group (39,11 ± 22,02 vs 24.83 ± 21,11 mg/day; p = 0.02).

Discussions

In this prospective observational study conducted in patients with ACHF, CRT allowed better implementation of carvedilol therapy and maintenance of high dose during long-term follow up. In these patients CRT associated to OMT yielded a significant improvement in NYHA functional class and LVEF. To date, at our knowledge, CARIBE-HF is the only prospective study to demonstrate that CRT can facilitate optimization of carvedilol treatment in patients with ACHF. Moreover, one of the strenghts of this study is related to the long-term follow-up achieved.

A wide difference in the increase of the carvedilol dose was seen over time; during the first phase of the study the dose was increased to a greater extent in NO-CRT patients than in CRT patients. This could be explained by the difference in clinical characteristics between two groups; at the beginning of the study, CRT patients had worse LV function and were more clinically unstable (more hospitalizations during the previous year, lower systolic blood pressure). These clinical and functional differences may in part be due to the presence of ventricular dyssynchrony. Indeed, the literature shows that the temporal alteration of

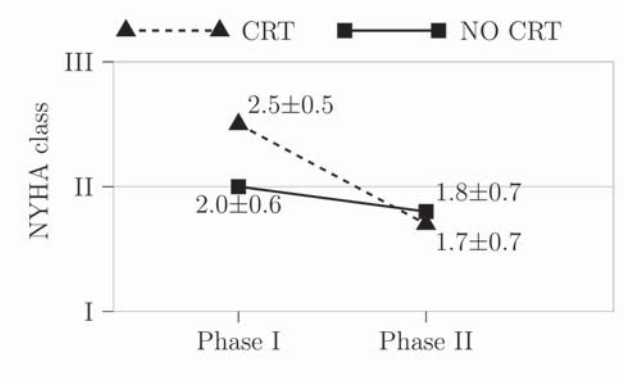

Figure 3a. *Variation in NYHA class from Phase I to II in CRT and NO-CRT groups (p=0.011)*

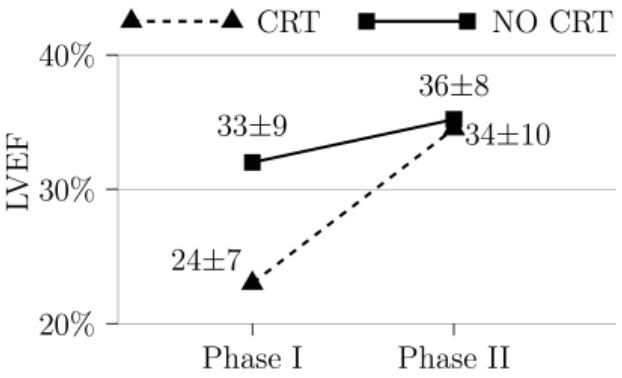

Figure 3b. *Variation in left ventricular ejection fraction from Phase I to II in CRT and NO-CRT groups (p=0.018)*

Table 3

Echocardiographic characteristics of the patients in the CRT and NO-CRT Groups

	Phase I			*Phase II*		
	CRT (15 pts)	*NO CRT (69pts)*	*P*	*CRT (15 pts)*	*NO CRT (69pts)*	*P value*
LV EDD (mm)	66±12	64±8	n.s.	63±12	63±10	n.s.
LV ESD (mm)	57±10	50±12	n.s.	51±14	53±10	n.s.
LV EDV (ml)	240±83	208±72	n.s.	212±76	206±74	n.s.
LV ESV (ml)	167±65	141±60	n.s.	146±74	133±60	n.s.
LV EF (%)	24±7	33±9	<0.001	34±10	36±8	n.s
MR (degree)	2.2±1.2	1.5±0.7	n.s.	1.4±0.9	1.5±0.9	n.s.
LVMP index	1.1±0.4	0.7±0.3	0.008	0.8±0.4	0.7±0.3	n.s.
RVMP index	0.6±0.6	0.5±0.3	n.s.	0.6±0.3	0.5±0.2	n.s.
E/A	1.5±0.5	1.0±0.5	n.s.	1.1±0.4	0.9±0.4	n.s.
DT	209±128	234±97	n.s.	240±107	258±94	n.s.

ventricular contraction can cause an increase in end ventricular stress and favor the process of apoptosis [20-21]. Moreover, unstable clinical conditions and hypotension, as well as bradycardia and AV block, typically represent a challenge in implementing betablocker therapy. particularly in patients with ACHF.

During the second phase of the study, when ventricular dyssynchrony was treated by bi-ventricular pacing, the carvedilol dose reached a significantly higher value, suggesting a positive effect of LV synchrony.

Clinical trials on beta-blockers have shown that inhibition of the beta-adrenergic system increases survival and quality of life in patients with HF [1-3, 5]. Reaching the optimal dose of carvedilol is one of the goals of medical therapy for HF. The MOCHA study demonstrated that the carvedilol-induced increase in LVEF is dose-dependent and is associated to better survival [22]; for this reason, its use at the target dose is strongly recommended by the international HF guidelines [23].

There is evidence that lack to achieve optimal medical therapy in HF is a major factor of hospitalization for worsening HF. However, as suggested by randomized clinical trials, only 52% of HF patients reach the maximal dose of beta-blockers [24]. The importance of achieving the optimal beta-antagonist dose is also suggested by the results of the two largest HF carvedilol studies: the Australia New Zealand Heart Failure Study [25] and the US Carvedilol Study [5]. In the former, carvedilol reduced mortality by 26%, while in the latter mortality was reduced by 65% [25]. This marked difference in survival may be explained by the different prevalence of patients who failed to reach the target dose (only 56% of patients in the Australia New Zealand Heart Failure study vs 85% in the US Carvedilol Study reached the target dose of beta-blockers).

In the Copernicus study, conducted in NYHA class III-IV HF patients [26], the target dose of carvedilol was reached in 65% of the cases only, compared with 85% in the US Carvedilol Study (NYHA II-IV) [5]; the difference (2.7 mg) between the average doses reached in the two studies was also significant. These data once again show that inhibition of the beta-adrenergic system in ACHF is usually reached with more difficulties and at lower doses of drug.

Increasing pharmacological compliance and the dose of carvedilol in HF patients at high mortality risk could further increase the benefits of beta-adrenergic inhibition. Only one study regarding the effect of CRT on beta-blocker therapy has been published [27]; in this retrospective analysis of 52 HF patients, Aranda et al. showed that 6 months after CRT the number of patients on beta-blocker therapy increased from 36 to 44, and that their clinical symptoms improved (NYHA functional class was reduced by 24%).

The use of an alternative therapy, such as CRT, to improve LV performance might facilitate pharmacological compliance with beta-blockers. In the CARIBE study, CRT was thought to have enabled the carvedilol dose to be increased through its beneficial clinical and functional effects. In patients

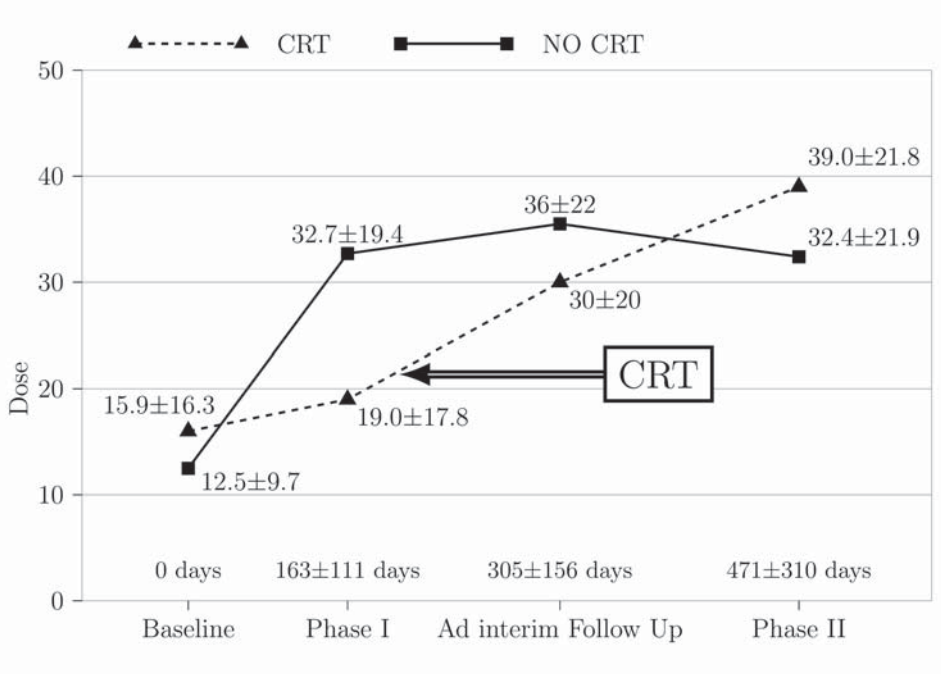

Figure 4. *Variations in carvedilol dose in CRT (p<0.0001) and NO-CRT groups (ns) during the phase I – phase II study*

with LV dyssynchrony and functional NYHA classes III – IV, CRT reduces hospitalization and mortality, and improves quality of life. Indeed, during the second phase of the study, CRT enabled the carvedilol dose to be raised significantly by 20 mg, while in the NO-CRT group the dose was decreased by 0.3. Furthermore, during the extended follow up the carvedilol mean dosage in CRT group was significantly higher. The favorable clinical effects are probably due to a synergistic effect of CRT and carvedilol.

Study limitations

As this study began in 2002, when the clinical use of biventricular devices had just been started, a limited number of patients were enrolled in the CRT group. Some difficulties arose regarding patient compliance, and a few patients were lost at follow-up. Despite the very long period of follow-up and the positive results of the statistical analysis, the small group of CRT patients precludes to reach definitive conclusions.

In 2002 knowledge of dyssynchrony criteria was limited and few studies involving tissue Doppler analysis had been published; for this reason, we assessed cardiac dyssynchrony according to the criteria proposed by the CARE-HF trial [14]. There was no statistical difference in heart rate (HR) between the 2 groups at the end of the study; but HR at rest is not as good an index of beta-adrenergic antagonism as exercise HR, which is considered more appropriate. Unfortunately, exercise HR was not assessed in the CARIBE study, as the majority of patients were unable to exercise because of their ACHF. Natriuretic peptides plasma levels are related with heart failure severity and in the CARE-HF after CRT implantation were decreased, but their determination was not routinely available when the present study began.

Conclusion

In patients with ACHF and reduced systolic function, it is difficult to reach the target dose of beta-blockers, owing to hypotension or unstable clinical conditions. If dyssynchrony criteria are present, CRT may create favorable conditions, which allow the doses of beta-blockers to be increased, thereby improving the clinical status and outcome. The results of the present prospective observational study, which used in ACHF a strategy of combining CRT and carvedilol, highlight a significant improvement in symptoms, reduction in functional class and increase in LV contractility.

Conflict of interest disclosure

S. Bisetti, T. De Santo, A. De Luca are employees of Medtronic, Italy.

No other conflict of interest exists.

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