ORIGINAL RESEARCH

Predictors of Positive Response to Resynchronization Therapy in Patients with Recurrent Episodes of Acutely Decompensated Advanced Heart Failure

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ABSTRACT

Background: In just a few years, cardiac resynchronization therapy (CRT) has emerged as a key player in the treatment of advanced heart failure (HF). However, approximately 30% of patients with CRT device implantation do not achieve a favorable response. The purpose of the present study was to identify clinical, electrocardiographic, and echocardiographic predictors of a positive response to biventricular pacing in patients with advanced decompensated HF. **Methods:** This prospective, observational study involved 42 consecutive patients admitted in emergency settings in our clinic with HF in New York Heart Association (NYHA) functional class III/IV, with QRS duration ≥120 ms and left ventricle ejection fraction (LVEF) ≤35%, who underwent cardiac resynchronization therapy (CRT-P or CRT-D) between January 2010 and July 2014. Statistical analysis was performed using IBM SPSS statistical software. **Results:** The clinical response (improvement in NYHA class) was recorded in 6 patients (14.3%), while echocardiographic response (change in ejection fraction and/or in end-systolic or end-diastolic volumes) was recorded in 10 patients (23.8%). The most frequently observed type of response to CRT was the double (clinical plus echocardiographic) response, recorded in 23 out of 42 patients (54.8%). ROC analysis identified the absence of chronic renal disease and the duration from onset of symptoms to CRT implantation as good predictors for clinical improvement after CRT (AUC = 0.625, 95% CI: 0.400−0.850 for absence of renal failure and AUC = 0.516, 95% CI: 0.369−0.853 for symptoms duration). However, gender, age, duration from symptom onset, and comorbidities were not good predictors for the echocardiographic response (AUC <0.600). **Conclusions:** CRT represents an important therapeutic option for selected patents with advanced decompensated HF and prolonged QRS interval; however, only some of the commonly used criteria can predict a favorable outcome in patients undergoing CRT.

Keywords: cardiac pacing, heart failure, resynchronization therapy

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BACKGROUND

Approximately 1–2% of the adult population in developed countries have heart failure (HF).[1–4] Its prevalence rises to ≥10% in those aged more than 70 years, representing approximately 4% from the total emergency hospital admissions.[2,3] In two-thirds of cases of systolic ventricular dysfunction, coronary artery disease (CAD) represents the main cause of HF; however, hypertension and diabetes can also represent likely contributing factors. The concept of biventricular stimulation in HF started from the frequent observation of intraventricular conduction delays in patients with HF and systolic dysfunction. In 25–50% of these patients, a large QRS complex with duration >120 ms is encountered, associated with a left-bundle block in 15–27% of the cases and with an atrial-ventricular asynchronism in 35% of the cases.[1–4]

The concept of cardiac resynchronization therapy (CRT) is based on synchronous stimulation of the ventricles using several intracardiac leads positioned in different sites in the heart and connected to a pulse generator. Nowadays, the selection of patients for CRT is based on electrical and electromechanical dys-synchronization criteria, which include electrocardiographic criteria (duration of the PR interval and morphology of the QRS complex, type of basic rhythm) and echocardiographic parameters (left ventricular ejection fraction [LVEF], size of the ventricles, presence and severity of mitral regurgitation, and intra- or interventricular asynchrony).[4,5]

Long-term clinical effects of CRT were evaluated in the last decade through randomized multicenter trials that showed the role of CRT in symptoms relief, improving effort-making capacity, and decreasing cardiovascular morbidity and mortality. Yet, despite the fact that indications for resynchronisation therapy are well described, selection parameters are still not well defined. Different studies showed that from the total number of patients who benefited from this technique, a percentage of up to 30% can be classified as non-responders, for complex and multifactorial reasons.[5–10] Furthermore, while the role of CRT has been well established for patients with chronic stable HF, little is known about the effects of CRT in patients with advanced decompensated HF, with severely depressed EF and advanced New York Heart Association (NYHA) stages, as most of these critically ill HF patients have been excluded from the major clinical trials on CRT.

The aim of the present work was to identify initial echocardiographic and clinical characteristics that predict a positive response to CRT in patients with advanced HF admitted in an emergency hospital for recurrent episodes of HF decompensation.

METHODS

PATIENT POPULATION

This prospective observational study included 42 consecutive patients admitted between January 2010 and June 2014 for recurrent episodes of acutely decompensated advanced HF and referred to the electrophysiology laboratory of the Cardiology Department of the Cardiovascular Disease Institute in Iași, Romania, for CRT implantation. As selection criteria for participating in this study, all patients were in NYHA functional class III/IV on optimal pharmacological treatment, presented a severely reduced left ventricular systolic function (LVEF ≤35%) and a QRS complex duration of >120 ms, and were in sinus rhythm.

Patients with a previously implanted pacemaker or defibrillator, recent myocardial infarction (<3 months), or recent coronary artery bypass surgery (<6 months) were excluded from the study.

All patients gave informed consent for participation in the study and ethical approval was obtained from the ethics committee of the institution.

In all patients, electrocardiographic characteristics including QRS duration and morphology were determined at rest using a 12-lead electrocardiogram (with a paper speed of 25 mm/s), immediately before and six months after CRT device implantation.

Clinical evaluation included assessment of NYHA functional class before and at the six-month follow-up after biventricular pacing.

Echocardiographic data were obtained using a conventional ACCUSON CV 70 System (Siemens, Erlangen, Germany). Echocardiography was performed in all patients at rest, in the lateral decubitus position, at baseline, before device implantation and six months later. A standard evaluation of left ventricular volumes was performed in the apical 4-chamber plane using the Simpson rule. The severity of mitral regurgitation was determined as the ratio between the maximum area of regurgitation flow in color Doppler testing and the area of the left atrium. Patients were classified as having mild (ratio <20%), moderate (20–40%), or severe (>40%) mitral regurgitation. To minimize the variability of measurements, all echocardiographic assessment were performed by the same physician.

DEVICE IMPLANTATION

The CRT device was implanted through the left subclavian and cephalic vein. Coronary sinus morphology was assessed prior to the procedure by angiography or computed tomography angiography. The left ventricular lead was inserted into the posterolateral vein with acceptable threshold stimulation in the absence of phrenic stimulation; the atrial lead was placed in the right atrial appendage, and the right ventricular lead was positioned in the right ventricular apex or ventricular septum. The device was programmed in DDDR stimulation mode and the atrioventricular and interventricular intervals were individually optimized after implantation.

DEFINITIONS

Patients were considered as responders if they exhibited an improvement of at least one NYHA functional class, an increase in LVEF by ≥5%, or a decrease of left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) by ≥15% at the six-month follow-up. If both clinical and echocardiographic improvement was noted, patients were classified as double responders. If none of these criteria was fulfilled, patients were classified as non-responders. Patients that presented an improvement of more than one NYHA class and an increase of LVEF with more than 10% at follow-up were classified as super-responders.

STATISTICAL ANALYSIS

Statistical analysis was performed using statistical functions in SPSS 18.0 at the significance threshold set at 95%. Primary processing and systematization of data by centralization and grouping led to primary indicators, which are presented as absolute sizes. On the basis of the primary indicators, by means of different statistical methods of comparison, abstraction, and generalization, derived indicators were obtained by the ANOVA test. Data are presented as average values (average arithmetic mean, median, module, minimum and maximum values) and dispersion indicators (standard deviation, coefficient of variation).

The t-Student test was used for comparison of the average values recorded in 2 groups with normal distributions, and F test (ANOVA) was used when comparing 3 or more groups with normal distributions. Pearson's correlation coefficient (r) was used for linear regression analysis, representing the correlation of 2 variables in the same group, the direct/indirect correlation being given by the coefficient sign. ROC analysis (Receiver Operator Characteristic) was used for analysis of the sensitivity/specificity balance of the tests.

RESULTS

The study population consisted of 36 males (85.71%) and 6 females (14.28%), with a mean age of 61.33 ± 10.4 years. Baseline characteristics of the study subjects are summarized in Table 1.

Baseline ECG analysis showed that the QRS complex had a mean duration of 178.8 ± 18 ms, with a left bundle brunch block (LBBB) morphology in most of the cases (95.24%), while only 4.76% of the cases presented a right bundle brunch block (RBBB) morphology. The etiology of the HF was ischemic cardiomyopathy in 23.81% of the cases.

Implantation of a CRT-D type was indicated in 19.04% of the patients for associated paroxysmal monomorphic ventricular tachycardia, while the rest of the subjects received a CRT-P type. According to inclusion criteria, all patients were in sinus rhythm and received optimum medical treatment as recommended by the guidelines, including beta-blockers, diuretics, angiotensin converting

TABLE 1.   Patient characteristics of the study population

Patient characteristics	Baseline (n = 42)
Age (years)	61.33 ± 10.4
Gender (male %)	85.71
DCM – ichemic n (%)	10 (23.81)
NYHA class IV n (%)	15 (36.42)
QRS duration (ms)	178.8 ± 18
CRT-D n (%)	8 (19.04)
LVEF (%)	20.85 ± 6.5
LVEDD (mm)	68.4 ± 6.5
LVESD (mm)	60.5 ± 4.2
LVEDV (mL)	236 ± 65.8
LVESV (mL)	185 ± 59.5
LAV (mL)	95.8 ± 16.5
ACE-I n (%)	36 (85.71)
ARB n (%)	6 (14.28)
Beta blockers n (%)	40 (95.23)
Diuretics n (%)	42 (100)
Aspirin n (%)	10 (23.81)
Warfarin n (%)	36 (85.71)

DCM – dilated cardiomyopathy; CRT-D – cardiac resynchronization therapy – defibrillator; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume; LAV – left atrial volume; ACE-I – Angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers

TABLE 2. Ventricular volumes in patients undergoing CRT

Parameter	N (%)	LVEDV (mL)			LVESV (mL)		
		Average ± SD	95% CI	p	Average ± SD	95% CI	p
All patients	42	268.55 ± 20.37	262.20−274.90	−	184.86 ± 9.72	181.83−187.89	−
Gender							
Males	36 (85.71%)	269.17 ± 19.83	262.46−275.88	0.635	185.06 ± 10.03	181.66−188.45	0.750
Females	6 (14.28%)	264.83 ± 25.13	238.46−291.20		183.67 ± 8.29	174.97−192.36	
Age							
<60 years	17 (40.47%)	266.65 ± 21.58	255.55−277.74	0.624	181.59 ± 8.18	177.38−185.79	0.072
≥60 years	25 (59.52%)	269.84 ± 19.86	261.64−278-04		187.08 ± 10.21	182.87−191.29	
Etiology of cardiomyopathy							
Ischemic	18 (42.85%)	271.11 ± 20.56	260.89−281.33	0.487	185.67 ± 10.32	180.53−190.80	0.646
Non-ischemic	24 (57.14%)	266.63 ± 20.46	257.98−275.27		184.25 ± 9.43	180.27−188.23	
NYHA class							
III	22 (52.38%)	265.41 ± 18.54	257.19−273.63	0.301	181.73 ± 9.10	177.69−185.76	0.027
IV	20 (47.61%)	272.00 ± 22.18	261.62−282.38		188.30 ± 9.42	183.89−192.71	
Duration from onset of symptoms to CRT							
<6 months	22 (52.38%)	274.32 ± 18.62	266.06−282.57	0.050	186.36 ± 10.63	181.65−191.07	0.298
≥6 months	20 (47.61%)	262.20 ± 20.78	252.48−271.92		183.20 ± 8.59	179.18−1887.22	

LVEDV – left ventricular end-diastolic volume; LVESV – left ventricular end-systolic volume

inhibitors, or angiotensin receptor blockers at maximum tolerated doses.

A significant number of patients presented associated comorbidities. Diabetes mellitus was identified in 28.6% of all patients and hypertension was present in 31% of the total cases. In our study population, 22.2% from those with ischemic etiology and 37.5% of those with non-ischemic etiology had a history of hypertension (p = 0.284). At the same time, 40.9% of patients in NYHA III class and 20% of those in NYHA IV class had a history of hypertension (p = 0.139). Chronic renal disease was present in 38.1% of the cases and obesity was present in 28.7%.

BASELINE ECHOCARDIOGRAPHIC CHARACTERISTICS OF THE STUDY GROUPS

Left Ventricular Ejection Fraction

Baseline ejection fraction ranged from 10 to 30%, averaging 22.40 ± 5.61%, close to the median value obtained for the entire study group, which was 22%, highlighting the homogeneity of the value series.

Assessment of intragroup characteristics in relation to LVEF at baseline showed no significant differences in LVEF in relation to gender (20.33% for females vs. 22.75% for males, p = 0.335), age groups (22.82% for younger than

60 years of age vs. 22.12% for older than 60 years of age, p = 0.695), type of cardiomyopathy (22.11% for ischemic vs. 22.63% for non-ischemic, p = 0.773), and time recorded since symptom onset (p = 0.630). However, patients in the NYHA IV functional class had significantly lower values of EF than those seen in NYHA III patients (18.65% vs. 25.82%, p = 0.001).

Left ventricular volumes

Left ventricular volumes in relation to subgroup characteristics at baseline are presented in Table 2. There were no significant differences of left ventricular end-diastolic volume (LVEDV) or end-systolic volume (LVESV) between different subgroups of gender, age, or type of cardiomyopathy. However, the mean LFEDV was significantly higher in patients less than 6 months after the onset of symptoms (274.32 mL vs. 262.20 mL, p = 0.05), while the mean LVESV was significantly higher in NYHA IV functional class as compared to NYHA III (188.30 mL vs. 181.73 mL, p = 0.027) (Table 2).

Left atrial volume (LAV)

Baseline LAV ranged from 72 to 187 mL, averaging 137.17 ± 30.33 mL. Similarly to the observations recorded for ven-

TABLE 3. Evolution of NYHA functional class post CRT

NYHA class post CRT	NYHA class before CRT			
	NYHA III		NYHA IV	
	N	%	N	%
NYHA I	4	18.2	0	0.0
NYHA II	11	50.0	4	20.0
NYHA III	6	27.3	10	50.0
NYHA IV	1	4.5	6	30.0

tricular volumes, there were no significant differences in the LAV in relation to gender (134.72 mL vs. 151.83 mL, p = 0.205), age groups (141.94 mL vs. 133.92 mL, p = 0.407), or etiology of DCM (139.17 mL vs. 135.67 mL, p = 0.716), while the mean LAV level was significantly lower in patients in NYHA III functional class (128.45 mL vs. 146.75 mL, p = 0.05) and in those with a time interval greater than 6 months from the onset of symptoms to acute decompensation (145.55 mL vs. 127.95 mL, p = 0.05).

DURATION OF QRS COMPLEX

Prior to the procedure, the duration of the QRS complex varied from 120 to 240 ms, averaging 160.48 ± 19.62 ms. There were no significant differences in the mean QRS in relation to gender (161.39 ms for males vs. 155 ms for females, p = 0.467), age groups (155.29 ms for younger than 60 years vs. 164 ms for older than 60 years, p = 0.161), etiology (162.78 ms for ischemic vs. 158.75 ms for non-ischemic, p = 0.517), NYHA functional class (157.73 ms for NYHA III vs. 163.50 ms for NYHA IV, p = 0.347), or time from onset of symptoms to acute decompensation (163.64 ms for shorter than 6 months vs. 157 ms for longer than 6 months, p = 0.279).

CRT type

Of the total 42 patients in the study group, 83.3% were treated with CRT-P and only 16.7% with CRT-D (Figure 1). Both CRT-P and CRT-D were more frequent in males (82.9% vs. 100%, p = 0.123), in those over 60 years (60% vs. 57.1%, p = 0.888), and in those living in an urban area (6% vs. 57.1%, p = 0.564).

FOLLOW-UP AFTER CRT FOR ADVANCED DECOMPENSATED HF

Functional capacity was significantly improved after CRT, most patients showing a significant improvement with at least one functional NYHA class at the one-month follow-up (Table 3).

In patients with ischemic cardiomyopathy, 55.6% recorded a decrease with one NYHA class and 11.1% with 2 NYHA classes, while 33.3% of them maintained the initial classification. From the subgroup with non-ischemic cardiomyopathy, 45.8% had a decrease with one NYHA class and 25% with 2 NYHA classes, while 25% retained their classification.

Left ventricular function and volumes at follow-up post CRT

At the 6-month follow-up, average LVEF recorded a significant increase from 22.40% to 29.98% (p = 0.001) (Figure 2).

In 76.2% of the patients, LVEF increased by at least 5%, with no significant differences between gender (36.68% for males vs. 42.32% for females, p = 0.699), age groups (34.68% for <60 years of age vs. 39.39% for >60 years of age, p = 0.6), or etiology (39.52% for ischemic HF vs. 35.96% for non-ischemic HF, p = 0.699).

Left ventricular volumes significantly decreased after CRT implantation (from 268.55 mL to 253.48 mL, p = 0.001 for LVEDV, and from 184.86 mL to 168.24 mL, p = 0.001 for LVESV) (Figure 3). The mean LVEDV decrease was slightly higher in females than in males (16.03 mL vs. 20.17 mL, p = 0.350), and a slightly higher average level was observed in the subgroup with over 60 years of age (14.53 mL vs. 18.04 mL, p = 0.265). However, there were no significant differences of LVESV in relation to gender (p = 0.237), age groups (p = 0.901), or duration from symptoms onset to presentation with decompensated HF (p = 0.293).
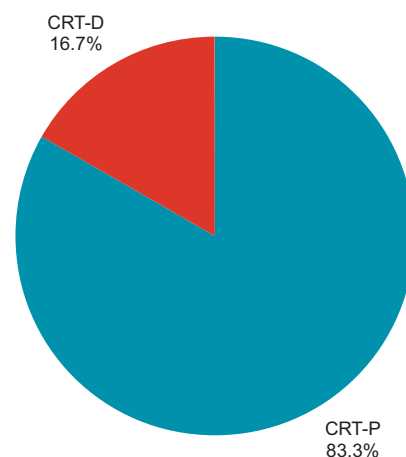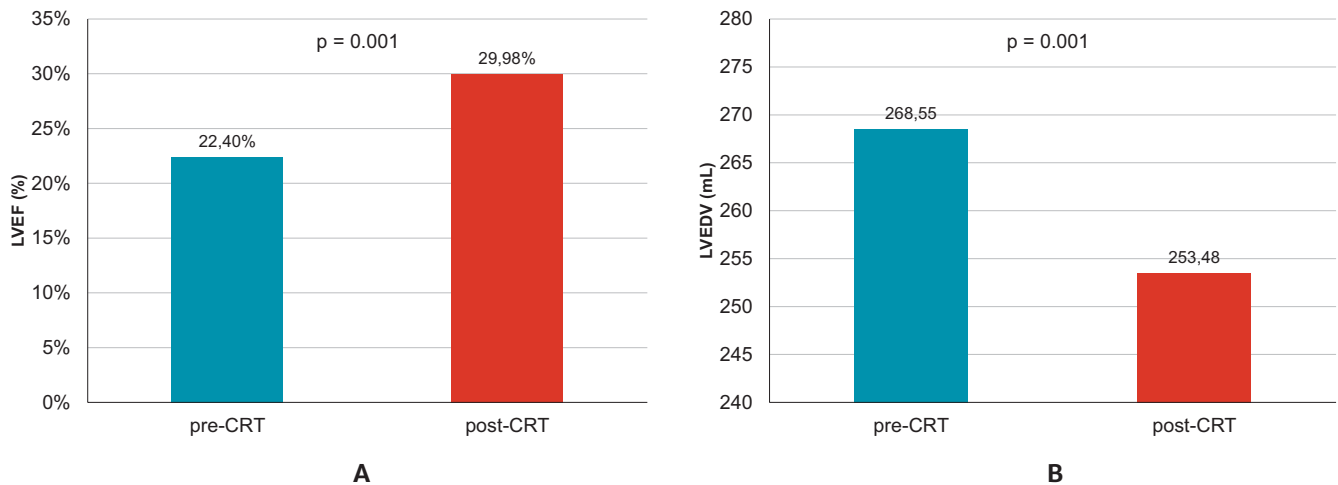

FIGURE 1. CRT type in the study population

FIGURE 2. Hemodynamic improvement post CRT; **A** – improvement in left ventriocular ejection fraction (LVEF); **B** – improvement in left ventricular end-diastolic volume (LVEDV)

Evolution of QRS duration post CRT

The QRS duration on the surface electrocardiogram decreased from an average value of 160.48 ms at baseline to 140.4 ms at follow-up, demonstrating a statistically significant correlation between the narrowing of QRS complex and the increase of LVEF (p = 0.001).

Type of responder pattern following CRT

Depending on the response to CRT, 6 patients (14.3%) were classified as clinical responders, showing improvement of NYHA functional class after CRT without any improvement in echocardiographic parameters, and 10 patients (23.8%) were classified as echocardiographic responders, demonstrating a significant improvement of LVEF, LVEDV, and LVESV post CRT without a significant clinical improvement. However, the most frequently observed response type in this study was the double response, encountered in 23 out of 42 patients (54.8%) who showed both clinical and echocardiographic improvement. Only 3 patients, who did not show any positive changes in either the NYHA functional class or the echocardiographic parameters, were classified as non-responders.

ROC analysis for prediction of clinical response to CRT

ROC analysis identified the absence of chronic renal disease and the duration from onset of symptoms to CRT implantation as good predictors for clinical improvement after CRT (AUC = 0.625, 95% CI: 0.400–0.850 for absence of renal failure and AUC = 0.516; 95% CI: 0.369–0.853 for

symptoms duration) (Figure 4A). However, gender, age, duration from symptom onset, and comorbidities were not good predictors for the echocardiographic response (AUC <0.600) (Figure 4B).

DISCUSSIONS

Cardiac stimulation seen as a complementary therapy for heart failure has been the subject of scientific research ever since the early 1990s.[4–12]

Long-term clinical effects of CRT were evaluated in the last decade through a large number of randomized multicenter trials such as MUSTIC-SR (Multisite Stimulation in Cardiomyopathy Study), MIRACLE (Multicenter In-Sync Randomized Clinical Evaluation Trial), COMPANION (Comparison of Medical Therapy, Pacing and Defibrilla-
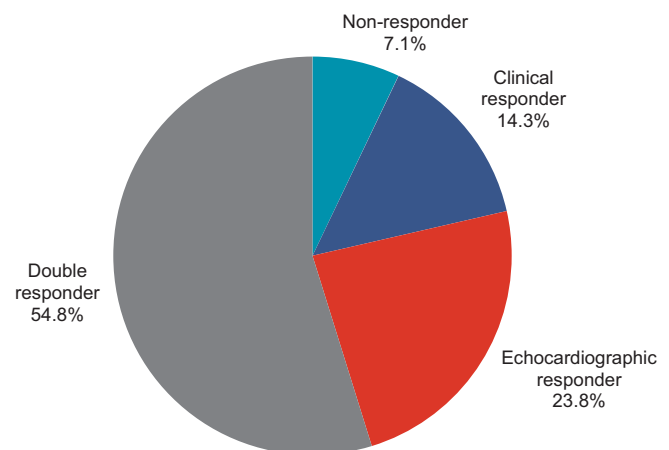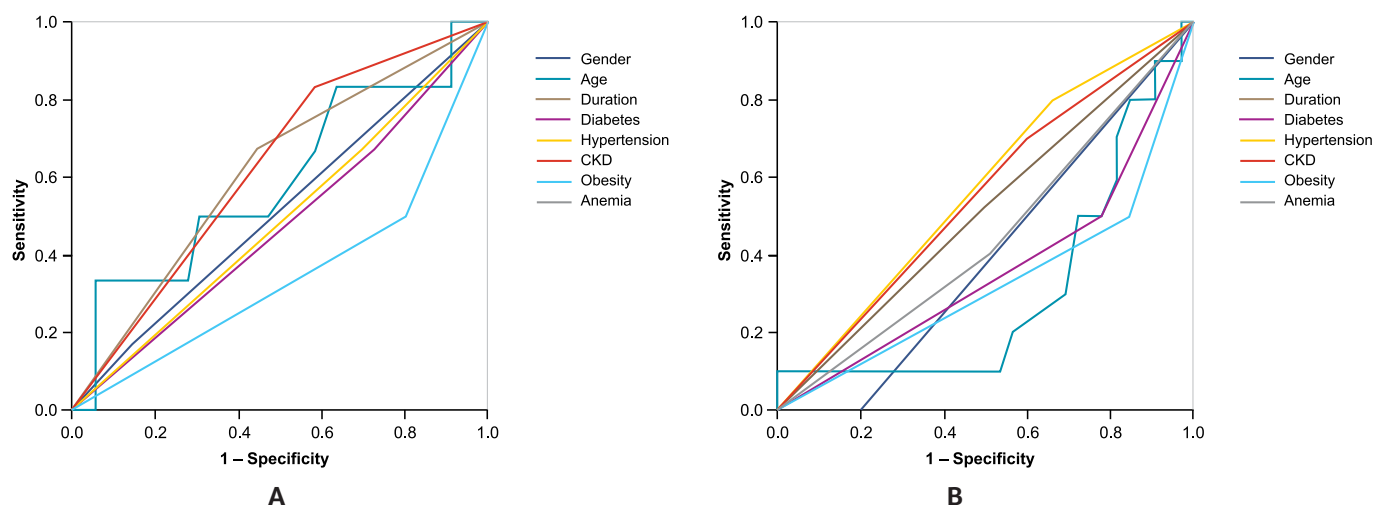

FIGURE 3. Type of response to CRT

FIGURE 4. ROC analysis of clinical parameters predicting response to CRT. **A** − Clinical parameters predicting clinical response (AUC = 0.406 for gender; AUC = 0.311 for age; AUC = 0.516 for duration; AUC = 0.359 for presence of diabetes; AUC = 0.572 for hypertension; AUC = 0.625 for chronic renal disease; AUC = 0.328 for obesity; AUC = 0.833 for anemia); **B** − Clinical parameters predicting echocardiographic response

tion in Heart Failure trial), or CARE-HF (The Cardiac Resynchronization Heart Failure trial), which demonstrated the role of CRT in symptoms relief, improvement of effort capacity, and decrease of morbidity and mortality in patients with HF.[13−16] Yet, despite the fact that indications for resynchronization therapy are well described, at present selection parameters are not well defined, so that studies revealed a percentage of up to 30% of non-responders in patients who benefited from this technique.[17−23] Therefore, we need more studies to investigate new options to reduce the frecvency of non-response to CRT and to improve the selection of patients for CRT.

In the current study, we succeeded to demonstrate that patients with advanced HF who present in an emergency hospital for recurrent episodes of decompensated HF and very low EF have a particular pattern of CRT response. The population of our study was characterized by a very low EF, with a mean value of 22.4%, indicating a severely ill group of advanced HF. Interestingly, we identified 4 types of CRT response in this critically ill group, and 38.1% of our study population showed a discordant clinical-echocardiographic response to CRT. We identified a subgroup of patients with clinical improvement in the absence of hemodynamic improvement (14.3%), as well as a subgroup with hemodynamic improvement in the absence of clinical improvement (23.8%).

It is important to note that patients with acute heart failure are usually excluded from major CRT trials, due to the potential risks associated with the implantation procedure in these critical cases and the high in-hospital mortality rates. The profile of our patient population is closer to the one of critically decompensated HF, as our patients presented a very compromised ventricular function with very low LVEF, as revealed by echocardiography. The multitude of compensatory mechanisms activated in different stages in the study group could be reflected in the variety of response to CRT therapy recorded in our study. However, the substrate that leads to the incomplete superposition of the clinical and echocardiographic responses to CRT has not been elucidated so far and needs further research.

LIMITATIONS OF THE STUDY

The study sample was relatively small and the duration of follow-up short. Further research is needed to provide data on the predictive characteristics for CRT response in advanced HF on a longer perspective.

CONCLUSION

CRT represents an important therapeutic resource for selected patents with advanced heart failure. However, only some of the commonly used criteria can predict the outcomes in patients undergoing CRT. This study revealed a good rate of clinical or echocardiographic response; however, the most frequently observed type of response was the double response. The absence of chronic renal disease and a shorter duration of symptoms proved to represent good predictors of clinical improvement following CRT in patients with recurrent episodes of advanced decompensated HF and low EF.

CONFLICT OF INTEREST

Nothing to disclose.

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