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Cardiac resynchronization therapy is effective even in elderly patients with comorbidities

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Abstract
Purpose The purpose of this study was to compare the effects of cardiac resynchronization therapy (CRT) in elderly patients (≥65 years) with younger patients and to assess the impact of comorbidities in CRT remodeling response.
Methods This is a prospective study of 87 consecutive patients scheduled for CRT who underwent clinical and echocardiographic evaluation before and 6 months after CRT. A reduction in left ventricular end-systolic volume (LVESV) ≥15% after CRT defined remodeling responders, and a reduction of at least one New York Heart Association class defined clinical responders. Multivariate analysis was used to identify independent predictors of non-response to CRT in terms of reverse remodeling.
Results The mean age was 62±11 years, with 36 elderly patients (41%). The baseline QRS duration was 145±32 ms. After CRT, there were significant and similar improvements of left ventricular (LV) ejection fraction, LVESV, LV dP/dt, and mitral regurgitation jet area (JA) between elderly (≥65 years) and younger (<65 years) patients. The number of clinical and remodeling responders was comparable, and we found no significant differences in unplanned cardiac hospitalizations at 6 months between groups. Independent predictors of lack of remodeling response to CRT were QRS duration <120 ms, LV diastolic diameter >74 mm, and JA >10 cm^2 before CRT, but not comorbidities.
Conclusion This work suggests that being elderly is not an impediment to CRT success even in the presence of comorbidities.

Keywords Resynchronization therapy · Elderly · Diabetes · Renal dysfunction · Hyperuricemia · Obesity

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1 Introduction

Heart failure (HF) is the fastest growing cardiovascular disease, and it carries a poor prognosis even with optimal pharmacotherapy [1]. The prevalence of HF increases rapidly with age, the mean age of HF population being around 75 years in developed countries [2, 3].

Cardiac resynchronization therapy (CRT) improves symptoms and also reduces HF hospitalizations and all-cause mortality when added to optimal pharmacotherapy in patients in New York Heart Association (NYHA) class III or IV, with reduced ejection fraction and a QRS width of at least 120 ms. However, in almost all randomized clinical trials, these results were demonstrated in selected patients, with few older patients enrolled [4–6]. As a result, it is still not completely clear whether elderly patients respond less favorably or not to CRT as compared with younger patients.

Conventionally, the term “elderly” has been defined as a chronological age of 65 years or older [7]. Recent studies have suggested that elderly patients derive similar benefits from CRT to younger patients [8–10]. Nevertheless, in these works, the elderly population is quite different in terms of chronological age: Foley et al. analyzed a population 80 or more years old; Bleeker et al. used 70 as cutoff, and Delnoy et al. studied a group older than 75 [8–11]. In addition, in these studies, there was no reference to comorbidities [8–10] or they were present in small rates in these older patients [11].

The aim of our study was to compare the effects of CRT in elderly patients (65 years or older) vs. younger patients (64 years or younger) in terms of clinical and echocardiographic parameters. We also aimed to assess the impact of typical heart failure-associated comorbidities in reverse remodeling and clinical response to CRT.

2 Methods

2.1 Inclusion criteria and study protocol

This is a prospective observational study that involved a single center. The study population included 87 consecutive patients with advanced HF who underwent CRT from November 2005 to October 2007. The majority of patients were in NYHA functional class III or IV despite optimal medical treatment. All patients had echocardiographic left ventricular (LV) ejection fraction <35% and QRS duration >120 ms (with left bundle branch block configuration) or QRS duration ≤120 ms, but mechanical dyssynchrony documented by tissue Doppler echocardiography (intraventricular dyssynchrony >40 ms and interventricular dyssynchrony >40 ms).

Patients were divided according to the chronological age into younger (less than 65 years old) and elderly patients (65 years old or older).

At baseline and 6 months after CRT, all patients underwent a clinical and echocardiographic evaluation. The clinical follow-up period was extended until 15th August 2009 (mean follow-up of 28±12 months), with hospital file review or direct telephone contact, and we have recorded the occurrence of death, heart transplantation, and hospitalization for heart failure management.

Regarding assessed comorbidities, estimated creatinine clearance (CrCl) was calculated with the Cockcroft–Gault formula and renal dysfunction was defined as a CrCl <60 ml/min. Hyperuricemia was defined as a serum uric acid level >7.0 mg/dl in men or >6.0 mg/dl in women. Patients with a body mass index of 30 kg/m^2 or higher were considered obese. We have also assessed history of known diabetes and persistent atrial fibrillation.

The protocol was approved by our institutional Research Ethics Committee, and all patients gave informed consent.

2.2 Device implantation

The LV pacing lead was inserted by a transvenous approach through the coronary sinus, with an over-the-wire system, into either a lateral or posterolateral cardiac vein whenever possible. The right atrium and right ventricle were stimulated by positioning standard bipolar leads in the right atrial appendage and right ventricular apex, respectively. A combined device (CRT plus internal defibrillator) was implanted in 64 patients (74%).

CRT device and lead implantation was successful in all patients, without major complications.

2.3 Echocardiography

Standard echocardiography, including tissue Doppler imaging (TDI), was performed using an ATL IDH 5500 Philips System (Vingmed- General Electric, Horten, Norway) before and 6 months after implantation of the biventricular pacing device. LV dimensions were measured from M-mode echocardiography in the parasternal long-axis view. The LV end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) were assessed by the biplane Simpson's equation in apical four-chamber and two-chamber views. Another measurement of systolic function evaluated was dP/dt. In fact, it has been demonstrated that the mean rate of Doppler-derived LV pressure rise during early systole (determined by the 1- and 3-m/sec velocity points on the rising segment of the continuous-wave mitral regurgitation curve) correlated well with peak dP/dt obtained from LV pressure curves at catheterization, although dP/dt may underestimate the true values in a substantial number of patients [12]. LV diastolic function was assessed with the evaluation of LV inflow diastolic velocities with pulse-wave Doppler (*E* and *A* velocities). We assessed the ratio of peak flow velocity in early diastole and peak flow velocity in late diastole during atrial contraction (*E*/*A*), the deceleration time of E-wave (DTE), isovolumic relaxation time, and the mitral regurgitation jet area (JA).

To assess dyssynchrony, time delay between the onset of QRS complex on the surface electrocardiogram and the onset of the systolic velocity wave on the TDI recording was assessed in four basal LV segments (septal, lateral, anterior, and inferior). Intraventricular dyssynchrony (TS-Intra-VD) was calculated as the difference between the longest and the shortest time delay in the four basal segments. Interventricular dyssynchrony (TS-Inter-VD) was calculated as the difference between time to peak systolic velocity at the right ventricle free wall and the most delayed LV segment.

One single operator performed all echocardiographic evaluations in order to avoid inter-individual variability.

2.4 Definition of CRT responders

At the 6 months of follow-up, patients were classified as clinical responders to CRT if they were still alive, had not been re-hospitalized for management of congestive heart failure, and had a reduction of at least one NYHA class. Regarding echocardiographic definition of response to

CRT, a decrease in LVESV of at least 15% defined remodeling responders [13].

2.5 Statistical analysis

Statistical analyses were performed using SPSS software version 15. Results are expressed as mean ± standard deviation (SD) for continuous variables and as counts and percentages for categorical variables. Data were compared with paired or unpaired Student's t test when appropriate. Nonparametric Mann–Whitney test was used for comparison of continuous variables between younger and elderly patients when variables were not normally distributed. Discrete variables were compared with the chi-square test or with Fisher exact test whichever is appropriate.

Efficacy of CRT was examined by comparing baseline vs. follow-up parameters using the Student's paired t test for comparisons of quantitative variables and by the McNemar test for comparisons of qualitative variables.

Independent predictors of non-response to CRT were identified by means of multivariable logistic regression. The simultaneous effects of elderly and comorbidities on non-response to CRT were examined. We entered into the multivariable logistic regression model the following variables: age over 65, renal dysfunction, diabetes, NYHA IV at baseline, left atrium >47 mm, QRS duration <120 ms, LVDD >74 mm, and JA >10 cm^2.

The Kaplan–Meier method was used to compare heart transplantation, death, or hospitalization for heart failure-free survival between elderly and younger patients.

A p value <0.05 was considered statistically significant.

3 Results

3.1 Study population

There were 55 male (63%) and 32 female patients (37%). The mean age was 62±11 years, with 51 younger patients (59%) and 36 elderly patients (41%). In the overall population, hyperuricemia was present in 49%, renal dysfunction in 38%, diabetes in 20%, obesity in 19%, and atrial fibrillation in 15% of patients. Baseline characteristics of the two age groups are summarized in Table 1. Elderly patients had a significantly higher prevalence of renal dysfunction (69.0% vs. 19.1%, p<0.001) and tend to have more diabetes. They also had less frequently a baseline QRS duration <120 ms (23.5% patients in the younger group vs. 6.1% in the elderly group, p=0.040), but LV dyssynchrony was similar in both groups (Table 1). The elderly group received less frequently a combined device (86% of the younger group vs. 56% of the elderly group, p=0.003). The left ventricular lead was positioned in a lateral or posterolateral vein in 73.3% of cases (75.0% of younger vs. 66.7% of elderly patients, p=0.645).

Table 1 Comparison of baseline characteristics between elderly and younger patients

Characteristics	<65 years old (n=51)	≥65 years old (n=36)	p value
Age	54.7±8.3	71.8±4.1	<0.001
Men/women (%)	66.7/33.3	58.3/41.7	0.501
NYHA class II	11.8	8.3	0.749
NYHA class III	64.7	72.2	
IV	23.5%	19.5%	
Ischemic/idiopathic (%)	33.3/66.7	38.9/61.1	0.653
QRS duration (ms)	141.2±33.1	150.0±28.4	0.212
Atrial fibrillation (%)	12.0	19.4	0.374
Diabetes (%)	13.7	29.4	0.077
Creatinine clearance (ml/min)	84.3±31.7	55.6±19.3	<0.001
BMI (kg/m^2)	27.5±4.1	27.4±3.6	0.836
Uric acid (mg/dl)	6.7±2.0	6.5±2.3	0.763
LVEF (%)	23.9±6.3	24.4±7.1	0.746
LVEDV (ml)	278.3±118.4	246.6±85.7	0.174
LVESV (ml)	214.2±102.5	188.2±71.7	0.192
LV dP/dt (mmHg/ms)	477.5±186.6	479.7±129.7	0.955
JA (cm^2)	7.9±5.9	7.6±5.1	0.821
E/A	1.4±0.8	1.1±0.5	0.097
DTE (ms)	169.6±62.5	174.6±70.3	0.323
Intraventricular dyssynchrony (ms)	81.7±46.2	84.2±56.2	0.821
Interventricular dyssynchrony (ms)	51.7±27.4	47.7±21.2	0.471

NYHA New York Heart Association, *BMI* body mass index, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LV* left ventricular, *JA* mitral regurgitation jet area, *E/A* E/A ratio, *DTE* deceleration time of E-wave

Table 2 Echocardiographic response over the two age categories

Six-month follow-up results	Younger (<65)	Elderly (≥65)
LV EF (%)		
Baseline	23.9±6.3	24.4±7.1
Follow-up	31.4±9.2*	31.0±9.9*
LVEDV (ml)		
Baseline	277.2±119.3	246.6±85.7
Follow-up	267.2±135.9	228.0±92.5*
LVESV (ml)		
Baseline	212.9±103.1	188.2±71.7
Follow-up	188.8±113.6*	161.9±79.7*
JA (cm^2)		
Baseline	8.1±5.9	7.6±5.1
Follow-up	6.2±5.1*	5.4±4.7*
LV dyssynchrony		
Baseline	81.7±46.2	84.2±56.2
Follow-up	44.4±34.3*	64.9±44.9
LV dP/dt (mmHg)		
Baseline	487.4±189.7	488.0±129.7
Follow-up	667.5±298.5*	701.7±259.1*

LVEF left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *JA* mitral regurgitation jet area, *LV* left ventricular

*$p<0.05$ (follow-up vs. baseline value)

3.2 Effects of CRT: 6 months of follow-up

After CRT implantation, there were significant improvements of LVEF, LVESV, LV dP/dt, and JA in both age groups (Table 2). Moreover, the magnitude of improvement of these echocardiographic parameters was not significantly different between groups. The reduction of LVESV was 24.1±43.1 ml in the younger group vs. 26.2±52.5 ml in the elderly group ($p=0.838$); the improvement of LVEF was 7.5±8.6% in the younger group vs. 6.5±9.2% in the elderly group ($p=0.621$); the improvement of LV dP/dt was 180.2±348.6 mmHg/ms in the younger vs. 217.7±269.1 mmHg/ms in the elderly group ($p=0.630$); and reduction of JA was 1.8±3.2 cm^2 in the younger vs. 2.3±4.0 cm^2 in the elderly group ($p=0.589$).

The number of remodeling responders and of clinical responders was comparable between younger and elderly patients (Fig. 1). During the 6-month follow-up period, we found no significant differences either in heart failure-driven rehospitalization or in ICD shocks between groups (Fig. 1). Only one patient underwent cardiac transplantation during the follow-up, and another one died due to heart failure.

3.3 Predictors of non-response to CRT

In the overall population, the proportion of remodeling non-responders to CRT was 46%. No significant differences between remodeling responders and non-responders to CRT were found regarding age, the incidence of diabetes, renal dysfunction, hyperuricemia, obesity, and the presence of ischemic cardiomyopathy. However, non-responders were more frequently in NYHA class IV before CRT (32.5% vs. 13% in remodeling responders, $p=0.038$), presented more frequently a QRS duration less than 120 ms (28% vs. 7%, $p=0.009$), with significantly larger baseline left atrium, higher LV dimensions and volumes, and greater mitral regurgitation JA than remodeling responders (Table 3).

In multivariate logistic regression analysis, independent predictors of non-response to CRT were baseline QRS duration less than 120 ms, LVDD higher than 74 mm, and JA over 10 cm^2 before CRT (Fig. 2). Comorbidities were not independent predictors of remodeling non-response to CRT.

In elderly patients, CRT response in terms of reverse remodeling was correlated to E/A ratio, E-wave deceleration time, LV dyssynchrony, and QRS duration. The E/A ratio was inversely correlated with the reduction of LVESV ($r=-0.602$, $p=0.001$). E-wave deceleration time, LV dyssynchrony, and QRS duration were directly correlated with LVESV reduction after CRT ($r=0.377$, $p=0.026$; $r=0.418$, $p=0.007$; and $r=0.378$, $p=0.021$, respectively).

None of the studied comorbidities was correlated with reverse remodeling after CRT in the elderly group.

3.4 Extended clinical follow-up

In the extended follow-up, the occurrence of heart transplantation, hospitalization for heart failure management, or death was verified in 27.6% of patients, with a mean time to this event of 14±10 months. The Kaplan–Meier survival analysis revealed no significant differences in event-free survival curves between the elderly and the younger groups (Fig. 3).

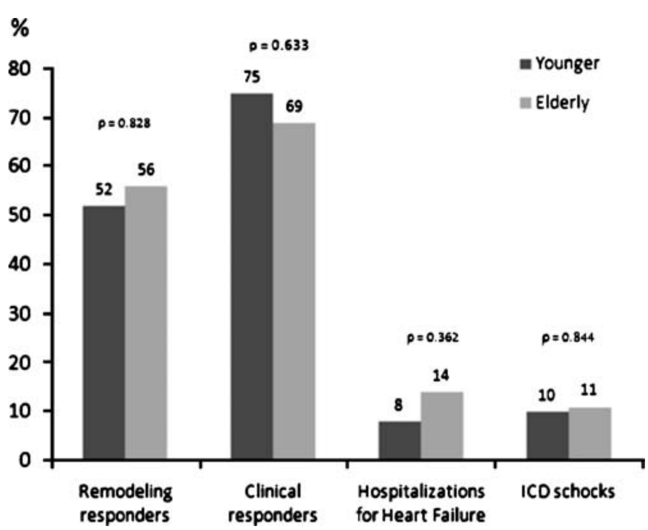


Fig. 1 Clinical outcomes over the different age categories

Table 3 Baseline characteristics of remodeling responders and non-responders to cardiac resynchronization therapy

	Responders	Non-responders	*p* value
Age	63±11	61±11	0.360
Men/women (%)	57/43	73/27	0.090
Baseline NYHA class (%)			
II	15	5	0.050
III	72	62	
IV	13	33	
QRS duration (ms)	150±30	139±33	0.110
Atrial fibrillation (%)	17.8	12.5	0.559
Ischemic/idiopathic (%)	34.8/65.2	35.0/65.0	0.983
Diabetes (%)	23.9	15.8	0.356
Renal dysfunction (%)	36.6	41.2	0.684
Obesity (%)	22.2	12.8	0.392
Hyperuricemia (%)	53.1	43.8	0.453
Left atrium (mm)	43±9	47±8	0.020
LVDD (mm)	71±7	79±11	<0.001
LVSD (mm)	59±7	67±12	0.001
LVEDV (ml)	237±73	296±130	0.009
LVESV (ml)	181±63	227±112	0.020
LVEF (%)	28±10	24±6	0.168
JA (cm^2)	6.0±4.8	9.9±5.8	0.001
LV dyssynchrony (ms)	84.5±57.6	80.4±41.7	0.710

NYHA New York Heart Association, *LVDD* left ventricular diastolic diameter, *LVSD* left ventricular systolic diameter, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction, *JA* mitral regurgitation jet area, *LV* left ventricular

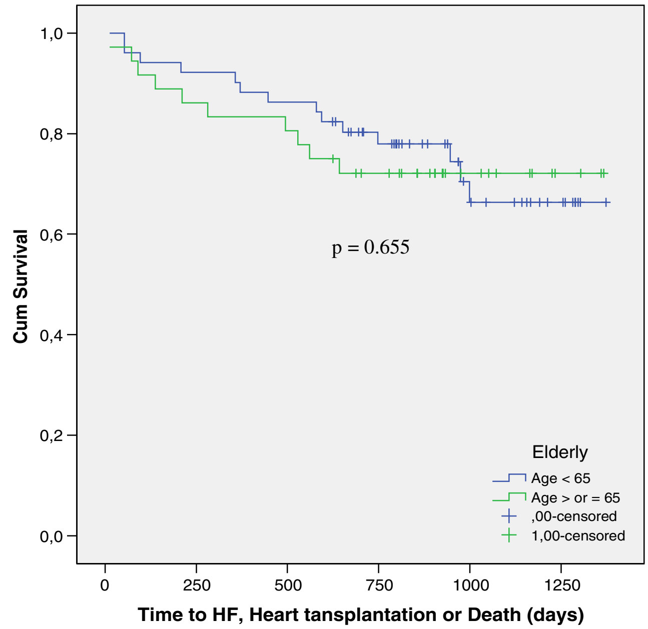


Fig. 3 Kaplan–Meier event-free survival of patients aged ≥65 and patients aged <65 years

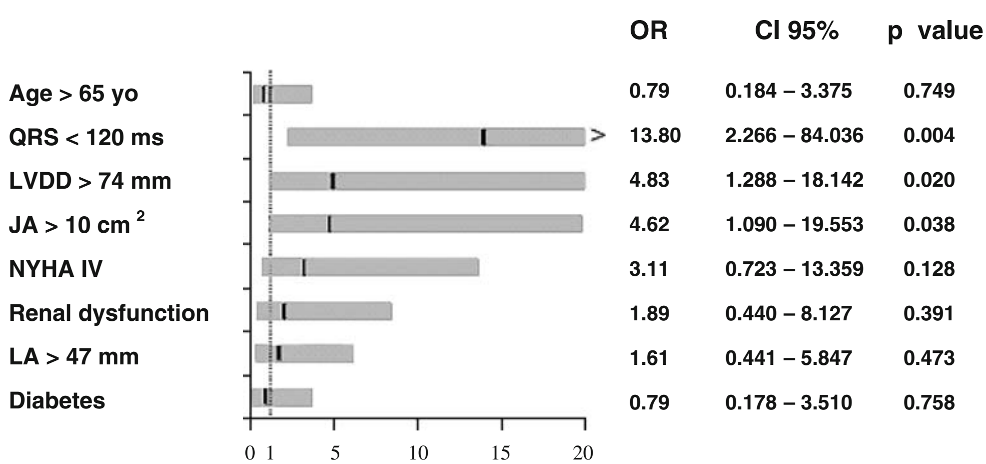
4 Discussion

Despite the encouraging results from CRT in recent trials, patients' responses to CRT vary significantly. Presently, it remains unclear whether or not elderly patients, of the real world, respond less favorably to CRT as compared with younger patients. If age was a negative influence on clinical outcome, this would be a good reason to restrict the use of CRT in the elderly.

Previous studies have shown that elderly patients with HF are a heterogeneous group and appear to differ substantially from patients enrolled in clinical trials [14]. Comorbidity complicates HF care and is prevalent in one form or another for the majority of elderly patients scheduled for CRT. This wide range of comorbidities, which includes diabetes and renal dysfunction, contributes to the progression of HF and may alter the response to treatment [15–17].

Previous data have demonstrated that the number and severity of comorbid illnesses is a key factor in the overall

Fig. 2 Multivariate logistic regression analysis of predictors of non-response to cardiac resynchronization therapy



survival of patients as well as the benefits of therapy [18]. So, we could ask: could comorbidities be an impediment to clinical and echocardiographic response to CRT?

In “the real world” clinical practice, elderly patients referred to CRT usually present comorbidities that distinguish them from the perfect candidate enrolled in clinical trials. Previous studies have looked at the impact of individual comorbidities or composite scores on mortality after CRT rather than their impact on CRT response [19, 20]. In fact, there are no studies that have examined the impact of comorbidities such as diabetes, renal dysfunction, obesity, and hyperuricemia on echocardiographic response to CRT, particularly in elderly patients. To the best of our knowledge, we were the first to do so.

4.1 Patient population

Several baseline characteristics of our study population were consistent with those of patients enrolled in previous CRT clinical trials, such as a predominance of male gender and NYHA functional class III, a marked systolic dysfunction as revealed by reduced LVEF, a severe LV dilatation, and a prolonged QRS duration. However, in our “real world” population, we had more patients over 65 years old than in previously published clinical trials [4, 6, 21–23].

In the elderly group, we observed several comorbidities that suggest that elderly patients were not selected on the basis of a special good clinical status.

4.2 Clinical outcome

At the 6-month follow-up visit, CRT resulted in significant benefits in both age categories, as evidenced by the improvement in clinical and echocardiographic parameters. CRT resulted in a significant improvement in LVEF and a left ventricular reverse remodeling. Moreover, the number of clinical and remodeling responders to CRT was similar in both groups, and there were no significant differences in unplanned cardiac hospitalizations within 6 months of CRT, thus supporting the hypothesis of an inducible favorable clinical effect and reverse remodeling even in older patients.

4.3 Impact of comorbidities

To the best of our knowledge, no data about the impact of comorbidities like renal dysfunction, obesity, and hyperuricemia in CRT response have been reported before.

One of the most important comorbidities in HF is renal dysfunction, and it is an important independent predictor of mortality and morbidity among this population [16]. Previous studies have indicated that CRT can be considered a renal-protective strategy in HF and that the improvement in renal function can be another mechanism to explain the beneficial effects of CRT [24–26]. Nevertheless, there are no studies in the literature that addressed the impact of renal dysfunction on the efficacy of CRT in terms of left ventricular reverse remodeling.

In our study, renal dysfunction tended to be slightly more prevalent in non-responders. However, in multivariate analysis, it was not a predictor of non-response to CRT. Even in elderly patients who had a higher prevalence of renal dysfunction, it seems not to prevent the positive response to CRT.

Heart failure and diabetes are strongly associated, and each condition represents a risk factor for the development of the other. Additionally, the presence of diabetes is a powerful independent predictor of morbidity and mortality among patients with HF [27]. The pathophysiology underlying HF in diabetic patients differs from that of non-diabetic patients, and it has been questioned whether CRT is equally beneficial in patients with and without diabetes. In accordance with previous studies, in our work, diabetes was not a predictor of poor response to CRT [28, 29].

Serum uric acid is intensively correlated with circulating markers of inflammation in patients with chronic HF and is a strong independent predictor of mortality. Inflammatory markers reflect HF severity, so we could speculate that high uric acid levels could be associated with a poor response to CRT. However, in our population, the proportion of hyperuricemic patients in remodeling responders was similar or even higher than that of non-responders.

Obesity represents an important risk factor for overall mortality and for development of HF in the general population [30]. Nevertheless, in patients with chronic HF, obesity appears to be associated with a favorable prognosis [31–34]. The underlying pathophysiology of this “obesity paradox” is still poorly understood. In the CRT setting, no previous studies have examined whether obesity affects or not the ability of left ventricular reverse remodeling. Our study is the first to do so, and it suggests that obesity is not an impediment to CRT positive response.

A recent meta-analysis of prospective cohort studies concluded that patients in atrial fibrillation show significant improvement after CRT, with similar or improved ejection fraction as sinus rhythm patients [35]. In accordance with previous study, in our work, atrial fibrillation did not appear to be a predictor of non-response to CRT.

In our work, comorbidities were not predictors of poor response to CRT, neither in the overall population nor in elderly patients.

4.4 Predictors of non-response to CRT

In our study, we included some patients with narrow QRS and mechanical dyssynchrony documented by echocardiography because at the beginning of this study, the results of the RethinQ study, providing evidence that patients with

HF and narrow QRS intervals may not benefit from CRT, were not yet known [36]. In our work, the stronger predictor of non-response to CRT was QRS less than 120 ms, which is in accordance with the results of the RethinQ study and suggests that CRT should not be offered to patients with a narrow QRS even if they present significant echocardiographic intraventricular dyssynchrony. LV dilatation and severe mitral regurgitation were the other predictors of lack of response, underlying the importance of LV geometry in reverse remodeling after CRT. It seems that patients with advanced forms of dilated cardiomyopathy are worse candidates for CRT than patients in the earlier phases of the disease.

In the elderly, mechanical dyssynchrony, again, seems to be crucial to a positive CRT response. In addition, in these patients, parameters of diastolic function were important factors for reverse remodeling. In our study, higher *E*/*A* ratios were associated with poor response to CRT, emphasizing the importance of cardiac compliance to achieve reverse remodeling.

4.5 Study limitations

This is a single-center, observational cohort study. The most important limitations of this study are the small number of patients included and the relatively short period of follow-up. Additionally, this work presents typical limitations of non-randomized studies that are a potential bias in patient's selection.

Another limitation of this study is the classification of diabetes that was made on the basis of medical history obtained from patients during the baseline visit interview; information on diabetic medications or diabetes control was not collected. Moreover, we did not ascertain cases of diabetes that developed during the study follow-up.

4.6 Clinical implications

Our work indicates that old age is not a reason for excluding patients from CRT. In fact, our study suggests that even elderly patients with comorbidities, but with good life expectancy, can benefit from CRT.

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