CLINICAL INVESTIGATIONS

Prognostic Role of Right Ventricular Function in Patients With Heart Failure Undergoing Cardiac Resynchronization Therapy

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Background: Because 20% to 40% of patients undergoing cardiac resynchronization therapy (CRT) do not respond to it, identification of potential factors predicting response is a relevant research topic.

Hypothesis: There is a possible association between right ventricular function and response to CRT.

Methods: We analyzed 227 patients from the Cardiac Resynchronization Therapy Modular Registry (CRT-MORE) who received CRT according to current guidelines from March to December 2013. Response to therapy was defined as a decrease of $\geq 15\%$ in left ventricular end-systolic volume (LVESV) at 6 months.

Results: The tricuspid annular plane systolic excursion (TAPSE) value that best predicted improvement in LVESV (sensitivity 68%, specificity 54%) was 17 mm. Stratifying patients according to TAPSE, LVESV decreased $\geq 15\%$ in 78% of patients with TAPSE > 17 mm (vs 59% in patients with TAPSE ≤ 17 mm; $P = 0.006$). At multivariate analysis, TAPSE > 17 mm was independently associated with LVESV improvement (odds ratio: 1.97, 95% confidence interval: 1.03-3.80, $P < 0.05$), together with ischemic etiology (odds ratio: 0.39, 95% confidence interval: 0.20-0.75, $P < 0.01$). These results were confirmed for New York Heart Association class III to IV patients (79% echocardiographic response rate in patients with TAPSE > 17 mm vs 55% in patients with TAPSE < 17 mm; $P = 0.012$).

Conclusions: Baseline signs of right ventricular dysfunction suggest possible remodeling after CRT. A TAPSE value of 17 mm was identified as a good cutoff for predicting a better response to CRT in patients with both mildly symptomatic and severe heart failure.

KEYWORDS

heart failure, remodeling heart failure, right ventricular function, cardiac resynchronization therapy

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure (HF) and systolic dysfunction. Despite the overall efficacy of CRT, up to one-third of eligible patients fail to derive significant clinical benefit from this therapy,^{1,2} and >40% do not show left ventricular (LV) reverse remodeling after the implantation of a biventricular pacing device. Several issues, either patient-related or procedure-related, may contribute to the lack of response to CRT: unfavorable anatomy or patient comorbidities, inadequate LV lead position,³ suboptimal device programming, suboptimal doses of β -blockers,⁴ low percentage of biventricular stimulation due to inhibition by intrinsic rhythm, failure to capture, or atrial and/or ventricular arrhythmias.⁵ It is therefore of paramount importance to identify factors that reliably predict a favorable response to CRT to reduce the rate of nonresponders.

Most of the studies on CRT have only described LV function, as CRT was primarily designed to improve LV contractility and synchrony. Impaired right ventricular (RV) function is an established marker of poor prognosis in patients with moderate to severe HF,^{6,7} and RV dysfunction has been associated with worse outcomes in patients undergoing the implantation of a biventricular pacemaker.⁸ The echocardiographic evaluation of RV systolic function may allow the contribution of the right chambers to CRT response to be assessed and may constitute a means of identifying CRT candidates who are more likely to benefit from this treatment.

The aim of the present study was to evaluate whether baseline RV systolic function, as assessed by tricuspid annular plane systolic excursion (TAPSE), was a predictor of response to CRT, as assessed by LV reverse remodeling, in a real-world population of patients with mild to severe symptoms of LV dysfunction and conventional indications for CRT.

2 | METHODS

2.1 | Study Population

The Cardiac Resynchronization Therapy Modular Registry (CRT MORE) is a prospective, single-arm, multicenter cohort study designed to evaluate the association between baseline and implantation variables and the outcomes of patients in a CRT population. All patients received a CRT device from March to December 2013 in accordance with current guidelines.⁹ The design of the study has been published previously.¹⁰ The study complies with the Declaration of Helsinki and was approved by the local institutional review board of each participating center. Informed consent was obtained from each patient. The present analysis was performed on all patients who had undergone a preimplantation and a 6-month echocardiographic evaluation. Patients with previous pacemaker/defibrillator implantation or permanent atrial fibrillation were excluded.

2.2 | Echocardiography

Echocardiographic evaluations were performed before CRT implantation and after approximately 6 months of CRT. Recordings were acquired by means of standard ultrasound systems (Vivid 7, GE

Vingmed Ultrasound, Horten, Norway; or iE33, Philips, Andover, MA). Data were obtained while the subjects were at rest in a lateral decubitus position. Three cardiac cycles were stored in a cine-loop format for offline analysis. Measurements of LV end-diastolic volume and LV end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were quantified by means of the Simpson biplane method. Tricuspid annular plane systolic excursion (TAPSE) was estimated on 2-dimensional echo-guided M-mode recordings from the apical 4-chamber view with the cursor placed at the free wall side of the tricuspid annulus to assess RV longitudinal function, as previously described.¹¹ Assessments of mitral regurgitation and RV functional impairment were made qualitatively and graded on a scale of 0 (none) to 4 (severe). The echocardiographic response to CRT was defined as $\geq 15\%$ reduction in LVESV or ≥ 5 unit increase in LVEF.

2.3 | Endpoints

The primary endpoint was the echocardiographic response to CRT defined as $\geq 15\%$ reduction in LVESV. The secondary endpoint was a worsened clinical status after 12 months. Patients were classified according to a clinical composite score that assigns subjects to one of 3 response groups—improved, worsened, or unchanged—as previously defined.¹² The clinical composite score describes patients as follows: (1) Worsened: patient dies, or patient is hospitalized owing to, or in association with, worsening HF; patient displays worsening in New York Heart Association (NYHA) class at the last observation carried out; patient reports moderate/marked worsening of the patient global assessment score at the last observation carried out; patient permanently discontinues CRT owing to, or in association with, worsening HF. (2) Improved: the condition of patient has not worsened (as defined above) and displays improvement in NYHA class at the last observation carried out or moderate/marked improvement in the patient global assessment score at the last observation carried out. (3) Unchanged: the condition of the patient has neither improved nor worsened.

2.4 | Statistical Analysis

Continuous data were expressed as mean $\pm$ SD or median (interquartile range). Comparisons of continuous variables between groups and within groups were made by means of unpaired and paired Student *t* tests, as appropriate. Comparisons of proportions between groups were made by means of the χ^2 or Fisher exact test. Receiver operating characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity of TAPSE in predicting LV reverse remodeling after CRT. A fixed cutoff of TAPSE value of 14 mm was also tested for prediction of CRT response in NYHA class III/IV patients for comparison with previous literature.¹³ To determine whether the TAPSE value before CRT was independently related to echocardiographic remodeling, a multivariate logistic regression model was applied in which baseline characteristics were controlled for. Predictors associated with a *P* value <0.1 on univariate analysis were entered into a multivariate analysis to identify independent predictors of the primary endpoint. The STATA/SE software version 12.1 (StataCorp LP, College Station, TX) was used for data analysis. A probability value of *P* < 0.05 was considered statistically significant.

TABLE 1 Demographics and Baseline Characteristics of the Study Population

Parameter	All Patients, N = 202	TAPSE ≤ 17 , n = 78	TAPSE > 17 , n = 124	P Value TAPSE ≤ 17 vs > 17
Age, y	70 $\pm$ 9	72 $\pm$ 8	69 $\pm$ 10	0.0453
Male sex	144 (71)	60 (77)	84 (68)	0.2133
BMI, kg/m ²	26.9 $\pm$ 6	26.5 $\pm$ 7	27.2 $\pm$ 6	0.5551
NYHA class				
II	93 (46)	27 (35)	66 (53)	0.0147
III	94 (47)	43 (55)	51 (41)	0.0723
IV	15 (7)	8 (10)	7 (6)	0.3465
Ischemic etiology	82 (41)	40 (51)	42 (34)	0.0211
COPD	52 (26)	16 (21)	36 (29)	0.2368
CKD	42 (21)	19 (24)	23 (19)	0.4164
DM	66 (33)	17 (22)	49 (40)	0.0139
HTN	128 (63)	49 (63)	79 (64)	0.9822
History of AF	59 (29)	32 (41)	27 (21)	0.0056
QRS duration, ms	162 $\pm$ 26	168 $\pm$ 28	159 $\pm$ 24	0.047
PR duration, ms	184 $\pm$ 39	190 $\pm$ 46	181 $\pm$ 36	0.4111
Conduction disturbance				
LBBB	164 (81)	57 (73)	107 (86)	0.0312 ^a
RBBB	22 (11)	12 (15)	10 (8)	0.1633
Nonspecific ICVD	16 (8)	9 (12)	7 (6)	0.2141
CRT-D device	183 (91)	75 (96)	108 (87)	0.0575
Pharmacological therapy				
ACEI/ARBs	150 (74)	59 (76)	91 (73)	0.8482
Diuretics	168 (83)	65 (83)	103 (83)	0.886
Statins	98 (49)	40 (51)	58 (47)	0.6315
β -Blockers	155 (77)	62 (79)	93 (75)	0.5729
Ivabradine	16 (8)	5 (6)	11 (9)	0.7167
Antiarrhythmics	41 (21)	18 (23)	23 (19)	0.5489
Echocardiographic data				
LVEF, %	28 $\pm$ 6	28.3 $\pm$ 6.5	29 $\pm$ 6.6	0.9889
LVESV, mL	136 $\pm$ 49	126 $\pm$ 47	138 $\pm$ 62	0.4901
LVEDV, mL	182 $\pm$ 68	175 $\pm$ 61	192 $\pm$ 75	0.306
MR grade ≥ 3	63 (31)	31 (40)	32 (26)	0.0541
TAPSE, mm	18.8 $\pm$ 5	13.5 $\pm$ 2.6	21.7 $\pm$ 3	< 0.0001
TR grade ≥ 3	11 (5)	6 (8)	5 (4)	0.4251

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; DM, diabetes mellitus; HTN, hypertension; ICVD, interventricular conduction delay; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RBBB, right bundle branch block; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Data are presented as n (%) or mean $\pm$ SD.

^aNot significant after Bonferroni correction.

3 | RESULTS

3.1 | Baseline Characteristics

The study initially considered 227 patients. Four patients died before reaching the 6-month follow-up examination (2 from HF; 2 for non-cardiovascular reasons). Moreover, we excluded 21 patients owing to inadequate RV echocardiographic images or lack of echocardiographic follow-up examination. Baseline clinical variables, echocardiographic parameters, and pharmacological therapies are shown in Table 1. Patients were predominantly male (144/71%) with a weak predominance of NYHA class III/IV (109/54%) and nonischemic etiology

(120/59%). A CRT defibrillator was implanted in 183 (91%) patients, and a CRT pacemaker was implanted in the remaining 19 (9%) patients. The mean value of TAPSE was 18.8 $\pm$ 5 mm, with an LVEF of 28% $\pm$ 6% and an LVESV of 136 $\pm$ 49 mL.

3.2 | Follow-up

At the 6-month follow-up examination, a significant decrease in LVESV (from 136 $\pm$ 49 mL to 99 $\pm$ 45 mL; $P < 0.001$) and a significant increase in LVEF (from 28% $\pm$ 6% to 37% $\pm$ 9%; $P < 0.001$) were observed. A reduction of $\geq 15\%$ in LVESV was found in 143 patients (71%), whereas 142 patients (71%) showed an absolute

FIGURE 1 Comparison of echocardiographic endpoint (LVESV↓15%; LVEF↑5%) at 6-month follow-up examination according to baseline TAPSE ≤17 mm vs baseline TAPSE >17 mm. Abbreviations: LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion.

increase of ≥5% in LVEF. At the 12-month follow-up examination, 31 patients (15%) displayed a deterioration in their HF clinical composite score, whereas 74 (37%) were classified as unchanged and the remaining 97 (48%) were classified as improved.

A nonsignificant association was found between LV remodeling, as assessed by reduction in the LVESV, and the degree of clinical composite status response. Considering the echocardiographic response as grouping factor, 72 (50%) of the 143 responder patients vs 25 (42%) of the 59 nonresponder patients displayed an improvement in their clinical status ($P = \text{not significant [NS]}$); 53 (37%) vs 21 (36%) remained unchanged ($P = \text{NS}$); and 18 (13%) vs 13 (22%) worsened their clinical status.

3.3 | Prediction of Response

A significant difference in the response to CRT was observed between patients with preserved RV function at the baseline and

those with impaired baseline RV function. On the basis of the ROC analysis, the cutoff value of TAPSE that best predicted LV reverse remodeling after 6 months of CRT was 17 mm (sensitivity 67.8%, specificity 54.2%; area under the curve: 0.615; $P = 0.0076$). Hence, TAPSE > or ≤17 mm was chosen as the cutoff to stratify the population into 2 groups according to baseline RV function. At the baseline, 124 (61%) out of 202 patients had a TAPSE value >17 mm. Accordingly, a decrease in LVESV ≥15% at 6 months was observed in 78% ($n = 97$) of patients with preserved baseline RV function vs 59% ($n = 46$) of those with baseline RV dysfunction ($P = 0.0056$; Figure 1). An absolute increase ≥5% in LVEF at 6 months was recorded in 76% ($n = 94$) of patients with preserved baseline RV function vs 62% ($n = 48$) of those with impaired baseline RV function ($P = 0.0452$; Figure 1).

The use of β -blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers was similar in the 2 groups, both at baseline and after 6 months of CRT. On univariate logistic analysis (Table 2), TAPSE ≥17 mm proved to be a significant predictor of favorable response to CRT in terms of LVESV reduction ≥15% at 6 months (odds ratio [OR]: 2.50, 95% confidence interval [CI]: 1.34-4.65, $P < 0.01$). By contrast, significant univariate predictors of non-response to CRT were mitral regurgitation (OR: 0.65, 95% CI: 0.43-0.98, $P < 0.05$) and ischemic etiology (OR: 0.32, 95% CI: 0.17-0.60, $P < 0.001$). On multivariate logistic analysis (Table 2), only TAPSE >17 mm and ischemic etiology remained independent predictors of CRT response, with an OR of 1.97 (95% CI: 1.03-3.80, $P < 0.05$) and 0.39 (95% CI: 0.20-0.75, $P < 0.01$), respectively. Among the 124 patients with a TAPSE value above the best cutoff, 15 (12%) displayed worsening in their clinical status after 12 months, as compared with 16 (20%) patients with TAPSE <17 mm ($P = \text{NS}$; Figure 2). This analysis was repeated on the overall study population (227 patients), including also patients who died before 6 months and patients with inadequate echocardiographic data at follow-up. Among the 138 patients with a baseline TAPSE value above the best cutoff, 21 (15%) displayed worsening in their clinical status after 12 months,

TABLE 2 Univariate and Multivariate Predictors of the Echocardiographic Endpoint (LVESV↓15%)

Variable	HR	95% CI	P Value	HR	95% CI	P Value
Age, y	1.0166	0.9838-1.0504	0.3268	—	—	—
Baseline LVEF	0.9821	0.9344-1.0322	0.4772	—	—	—
Baseline QRS	0.9949	0.9830-1.0068	0.3987	—	—	—
Baseline TAPSE	1.0867	1.0169-1.1612	0.014	—	—	—
Baseline TAPSE above cutoff	2.4992	1.3433-4.6498	0.0038	1.9731	1.0256-3.7959	0.0418
Cr level	0.5999	0.2851-1.2619	0.178	—	—	—
DM	1.1154	0.4955-2.5109	0.792	—	—	—
Male sex	0.5384	0.2609-1.1111	0.094	0.6002	0.2718-1.3252	0.2065
History of AF	0.8675	0.3799-1.9813	0.7359	—	—	—
Ischemic etiology	0.303	0.1614-0.5689	0.0002	0.3854	0.1986-0.7477	0.0048
LBBB	1.4194	0.5825-3.4586	0.4409	—	—	—
RBBB	0.5217	0.1570-1.7343	0.2884	—	—	—
MR grade	0.6189	0.4054-0.9447	0.0262	0.663	0.4181-1.0515	0.0807
NYHA class	0.7535	0.4640-1.2235	0.2525	—	—	—

Abbreviations: AF, atrial fibrillation; CI, confidence interval; Cr, creatinine; DM, diabetes mellitus; HR, hazard ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RBBB, right bundle branch block; TAPSE, tricuspid annular plane systolic excursion.

FIGURE 2 Clinical composite score response according to baseline TAPSE stratified by best cutoff point ($n = 202$). Abbreviations: NS, not significant; TAPSE, tricuspid annular plane systolic excursion.

as compared with 20 (23%) of the 89 patients with TAPSE <17 mm ($P = \text{NS}$). The analysis of this population confirmed the findings obtained in the 202 patients included in the primary-endpoint analysis. In our population, LV remodeling was comparable in NYHA class II (74%) and NYHA class III/IV patients (68%; $P = \text{NS}$). At the 6-month follow-up examination, a significant increase in RV function, as assessed by TAPSE, was observed in the overall population (from 18.8 ± 5 mm to 19.5 ± 4 mm; $P = 0.037$). Right ventricular function at 6 months was significantly higher in responder patients than in nonresponder patients (18 ± 4 mm vs 20 ± 4 mm, respectively; $P = 0.0031$).

3.4 | Comparison With Previous Evidence in New York Heart Association Class III/IV Recipients

For this analysis, a cutoff of TAPSE of 14 mm was applied in NYHA class III/IV patients. In our population, a TAPSE value of 14 mm did not allow to stratify echocardiographic responders and nonresponders (73% vs 56%; $P = 0.1126$). To investigate the ability of TAPSE to predict echocardiographic response in this specific population, ROC analysis was repeated. Optimal sensitivity and specificity were obtained with a cutoff value of 17 mm (62% and 66%, respectively; area under the curve: 0.631; $P = 0.0197$). The NYHA class III/IV patients with a baseline TAPSE above the cutoff showed a 79% echocardiographic response rate, as opposed to 55% in patients with TAPSE <17 mm ($P = 0.012$).

4 | DISCUSSION

In this study, we investigated the predictive role of the preimplantation TAPSE value in a population of patients with HF on optimal medical therapy who underwent CRT. Right ventricular dysfunction, as measured by TAPSE, was associated with a worse outcome. Right ventricular function is known to correlate with outcome in HF patients. Assessing RV function is clinically challenging, owing to the complex geometry of the chamber and difficult visualization on standard echocardiography. Right ventricular systolic function is also difficult to assess, owing to the complex anatomy and shape of the chamber. Magnetic resonance imaging (MRI) has proved to be an

accurate imaging technique for estimating RV volumes and function.¹⁴ In clinical practice, however, it is neither quickly available nor feasible in all patients. By contrast, TAPSE is an easily obtainable, highly reproducible, and reliable index of RV function, and it has been shown to have a high predictive value in patients with HF.¹⁵ Furthermore, TAPSE correlates highly with volumetric quantification of the RV ejection fraction on MRI,¹⁶ whereas both 2D and 3D echocardiographic estimates of RV size and RV ejection fraction display only a moderate correlation with MRI measurements of these parameters.¹⁷ Therefore, for routine clinical purposes, TAPSE may be the preferred technique for evaluating RV function.

Recently, Scuteri et al demonstrated a significant correlation between echocardiographic indexes of baseline RV function and the degree of LV reverse remodeling observed 6 months after CRT in a small cohort of patients with HF. Moreover, a subgroup of patients with markedly reduced RV longitudinal motion, as measured by a TAPSE value <14 mm, exhibited significantly less LV reverse remodeling after CRT, regardless of satisfactory mechanical resynchronization after device implantation.¹⁸ Of note, previous evidence suggested that a TAPSE cutoff of 14 mm should underestimate the likelihood of response to CRT in patients with mild symptoms of HF.¹⁹ In the present study, we correlated baseline RV function and CRT response in CRT recipients. In our cohort, we found a correlation between TAPSE values and CRT response in terms of LVESV reduction (TAPSE cutoff 17 mm). On multivariate analysis, only TAPSE >17 mm and ischemic etiology were confirmed to be independent predictors of CRT response. Our data show that, in mildly symptomatic HF patients who are candidates for CRT, RV function is able to predict a positive response to the therapy. Recently, a subanalysis of the Cardiac Resynchronization in Heart Failure (CARE-HF) trial showed that RV dysfunction was a powerful determinant of prognosis after CRT but did not reduce the prognostic benefits of CRT.²⁰ On the other hand, there is other evidence in the literature that CRT response is not dependent on TAPSE.¹⁹ However, in these studies, the authors pre-specified a cutoff value of 14 mm to identify RV dysfunction. This could be misleading, because this value is actually associated with markedly reduced RV function and does not take into account various degrees of RV impairment. Our data identify a cutoff value of 17 mm, both in mildly symptomatic HF patients and severe HF patients, which is able to predict a better response to CRT. This confirms the findings of a previous single-center experience involving a limited number of patients.²¹

In another study, Damy et al divided CRT recipients into tertiles and found that RV dysfunction was associated with a worse prognosis but did not correlate with a reduced clinical response to CRT.²⁰ However, dividing the population of CRT recipients into tertiles is not based on any analysis that would correlate RV function with CRT response and can be considered somewhat arbitrary. Moreover, the number of patients with less severe HF in terms of NYHA class was much higher in our cohort than in the patients studied by Damy and colleagues. Therefore, one could speculate that, in patients with very advanced disease, the impact of RV function as a predictor of CRT response could be underestimated because of the scant functional reserve of the whole heart. Regarding RV reverse remodeling after CRT implantation, we did not find any amelioration of RV function, as

measured by TAPSE, at the 6-month follow-up examination. This confirms previous findings.²⁰ On the other hand, we cannot exclude the possibility that longer follow-up could be required to detect an improvement in RV function. Indeed, the improvement in RV function could be a consequence of the reduction in mean pulmonary arterial pressure and might take place only after LV reverse remodeling.

4.1 | Study Limitations

In the absence of a control group that did not receive CRT, we cannot determine whether the benefit of CRT is specifically attenuated by RV dysfunction. Nevertheless, this study demonstrates that, in a population of patients with LV systolic dysfunction, TAPSE predicts response to CRT. Because this index requires no specialized echocardiographic equipment, its routine quantification should be recommended to identify HF patients more prone to respond to resynchronization. We did not find any reduction in terms of major cardiovascular events. Indeed, we did not demonstrate that a reduced baseline TAPSE value in patients treated with CRT was associated with a poor clinical response and/or adverse prognosis. Patients with poor RV function showed a slight, but not significant, clinical deterioration from baseline to follow-up examination in comparison with those with preserved RV function. However, this could be related to the relatively short duration of the follow-up.

5 | CONCLUSION

In the present study, we identified a TAPSE cutoff value that is able to predict a better response to CRT in both mildly symptomatic HF patients and severe HF patients. Despite the lack of a difference in the composite clinical score, we found a significant difference in the proportion of patients showing a reduction in LVESV after CRT, and this is also a promising result in terms of long-term prognosis.

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