Cardiac resynchronization therapy improves functional status and cognition at long-term follow-up

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DOI: 10.33963/v.phj.108186

Received:
April 24, 2025

Accepted:
August 19, 2025

Early publication date:
August 19, 2025

INTRODUCTION

Cardiac resynchronization therapy (CRT) significantly reduced mortality and heart failure (HF) hospitalizations in patients with HF with reduced ejection fraction, left bundle branch block, and left ventricular ejection fraction (LVEF) ≤35%, who were still symptomatic despite optimal medical therapy [1–3]. In the attempt to identify patients who are more likely to derive clinical benefit from this invasive tool, several studies attempted to look for criteria and predictors of CRT "response" [4–8]. A significant proportion of patients lacking LV reverse remodeling still experience a significant improvement in symptoms and functional status [9].

In a previous study we demonstrated that CRT was associated with higher functional and cognitive profile after only 6 months of therapy [10]. The purpose of this study is to evaluate CRT effects on cognition, functional performance, and psychological profile at long-term follow-up.

MATERIAL AND METHODS

We prospectively enrolled all consecutive patients in three Italian centers, undergoing implantation of devices for CRT (CRT-P) or CRT and defibrillation (CRT-D), who met the following criteria: symptomatic HF with reduced ejection fraction (New York Heart Association class II to class IV) despite optimal medical therapy, LV systolic dysfunction with LVEF ≤35%, QRS width ≥130 ms, and left bundle branch block morphology. Responder status was defined as ≥15% increase of LVEF and/or by ≥15% reduction of LV end-systolic volume. All patients underwent a cardiologic evaluation before CRT implantation at 6- and 30-month follow-up. At baseline and at each follow-up, a battery of tests exploring functional, neurocognitive, and psychological profile was administered. Cognitive profile was assessed using the Mini-Mental State Examination (MMSE) and the Trail Making Test (TMT) A and B. Functional profile was determined with the Short Physical Performance Battery (SPPB) measuring balance, gait speed, and strength/endurance [11]. Psychological profile was evaluated using the Profile of Mood States rating scale (POMS), the Pittsburgh Sleep Quality Index, and the Personal Health Questionnaire Depression Scale (PHQ-8) [10]. The institutional review board of each center approved the protocol, which conforms to the 1975 Declaration of Helsinki.

Statistical analysis

Data were analyzed with IBM SPSS Statistics (version 29; Armonk, NY, US). Continuous variables are expressed as mean (standard deviation). Normality of continuous variables was assessed with the Kurtosis statistic. General linear models for repeated measures were used to evaluate the outcome variables from baseline to the 6- and the 30-month observation. In the case of a statistically significant trend, a *post hoc* contrast between the 6- and 30-month value with the baseline value was performed, applying a non-parametric test (the Wilcoxon signed-rank test) in the case of TMT A and B, total POMS score, and

PHQ-8 score, which showed a non-normal distribution. TMT A and B, total POMS score, and PHQ-8 score were summarized using the median and interquartile range (IQR). Categorical variables are reported as raw data and percentages, with the χ^2 test evaluating the presence of different distributions. Due to a relatively small sample size, *P*-values were estimated using exact test procedures when appropriate. All univariate determinants of changes in the SPPB total score were entered into a multivariable linear regression analysis model using backward deletion to identify the best-fitting set of variables associated with physical performance improvement. Accordingly, based on the size of our population (n = 43 patients), a retrospective analysis indicated a statistical power greater than 80% ($\alpha = 0.05$, two-tailed), corresponding to an effect size of 0.53.

RESULTS AND DISCUSSION

Baseline characteristics

We enrolled 54 patients (men: 80%; age: 67 [10] years), 3 of whom (5.5%) died during the follow-up. All events were due to non-cardiac causes. Eight patients (14.8%) withdrew their consent to participate. Accordingly, the results presented refer to the remaining 43 subjects. All variables analyzed are shown in Supplementary material, *Table S1*.

Overall, 18 patients (43%) had an ischemic etiology; baseline LVEF was severely reduced in 28 patients (5%). Mean Charlson Comorbidity Index was 4.3 (2.1). Medical therapy for HF was almost optimal according to the real-world clinical setting (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/sacubitril–valsartan: 84%; β-blockers: 80%; aldosterone antagonist: 65%). Overall, patients received 7.2 (2.2) drugs per day. At baseline, MMSE performance was lower than normal, with only 18 patients (36.0%) scoring at least 27 points. The percentage of CRT biventricular pacing was high (median: 97%; 25^{th}–75^{th} percentile: 93%–99%); 8 patients (18%) had atrial fibrillation, and 7 of them underwent atrioventricular junction ablation during the study period in the first 6 months.

Effects of CRT at 30-month follow-up

LVEF progressively improved with CRT from baseline to the 30-month evaluation (baseline: 28 [5]% vs. 6-months: 35 [8]% vs. 30 months: 39 [9]%; *P*-trend <0.001) with no sex differences. CRT also determined a reverse LV remodeling, with reduction of LV end-diastolic diameter (baseline: 68 [8] mm vs. 6-months: 65 [8] mm vs. 30 months: 65 [10] mm; *P*-trend = 0.04) and of LV end-systolic diameter (baseline: 57 [9] mm vs. 6-months: 50 [9] mm vs. 30-months: 50 [12] mm; *P*-trend = 0.002). CRT therapy was associated with significant improvement of physical performance, as reflected by the increase of the SPPB, in its total score, and in the Gait Speed and in the Chair Stand partial scores (Figure 1A–C). No differences in the SPPB balance-test were observed (baseline: 3.3 [1.0] vs. 6 months: 3.6 [0.7] vs. 30-months: 3.4 [1.1]; *P*-trend = 0.20). MMSE was higher than baseline at the 6- and 30-month evaluations (Figure 1D). The proportion of patients with a better cognitive performance was greater among those with an abnormal baseline score (<27: 71.6% vs. 27–30: 30.2%; *P* = 0.01). To confirm these findings, the time needed to complete both TMT A and TMT B progressively reduced (Figure 1E–F). Also, after 30 months, we showed improvement of depressive symptoms (PHQ-8 median, IQR; baseline: 7 [3–9] vs. 6-month: 4 [2–8] vs. 30-months: 4 [2–7]; *P*-trend = 0.03) and sleep quality (Pittsburgh Sleep Quality Index; baseline: 7.9 [5.4] vs. 6--month: 5.5 [4.2] vs. 30-month: 5.5 [4.5]; *P*-trend = 0.02). In the multivariable linear regression analysis model, age ($\beta_{\text{per year}} = 0.042$; 95% CI, 0.006–0.078; *P* = 0.02) and allopurinol therapy ($\beta_{\text{yes vs. no}} = 1.508$; 95% CI, 0.522–2.494; *P* = 0.002) were positively correlated with SPPB improvement at 30 months, while LV end-systolic volume ($\beta_{\text{per ml}} = -0.017$; 95% CI, –0.026 to 0.008; *P* = 0.003), the time to complete TMT A ($\beta_{\text{per s}} = -0.006$; 95% CI, –0.010 to 0.002; *P* = 0.01), and the SPPB score itself ($\beta_{\text{per baseline score point}} = -0.567$; 95% CI, –0.731 to 0.403; *P* <0.001) showed an inverse association with the variable. These data confirmed and extended our previous 6-month experience [10], showing that CRT is associated with an improvement of lower extremity function and of neurocognitive performance also in the long-term. While most improvements in functional and cognitive performance occurred during the first 6 months after CRT implantation, further stabilization or modest additional gains were observed over the subsequent 24 months, suggesting a sustained benefit over time. Despite robust clinical evidence, CRT remains underused — particularly in New York Heart Association class II patients, in whom earlier intervention may help delay or even reverse disease progression [12]. Changes in cognition were even more evident in subjects with a lower MMSE score at baseline. Similar observations have recently been reported in post-infarction patients, where cognitive dysfunction was present in over one-third of cases and persisted in a significant proportion after 6 months [13]. A better physical, functional, and cognitive condition was also associated with fewer depressive symptoms and enhanced sleep quality. Based on these assumptions, we could hypothesize that the traditional concept of CRT "response", only centered on cardiological variables, could be enriched and extended, taking into consideration the positive changes of functional and cognitive status [14]. However, we cannot exclude a possible synergistic or independent contribution of medical therapy to the observed improvements — we believe that CRT exerts additional, measurable effects, particularly in frail or cognitively vulnerable patients, which extend beyond what medications alone are likely to achieve. The effects of drugs for HF and CRT are possibly additive and counteract numerous mechanisms linked to the onset of dementia in the HF setting, encompassing cerebral hypoperfusion, hypoxia, progression of small vessel diseases, and proliferation of neurodegenerative changes in the brain. Medical therapy for HF was almost

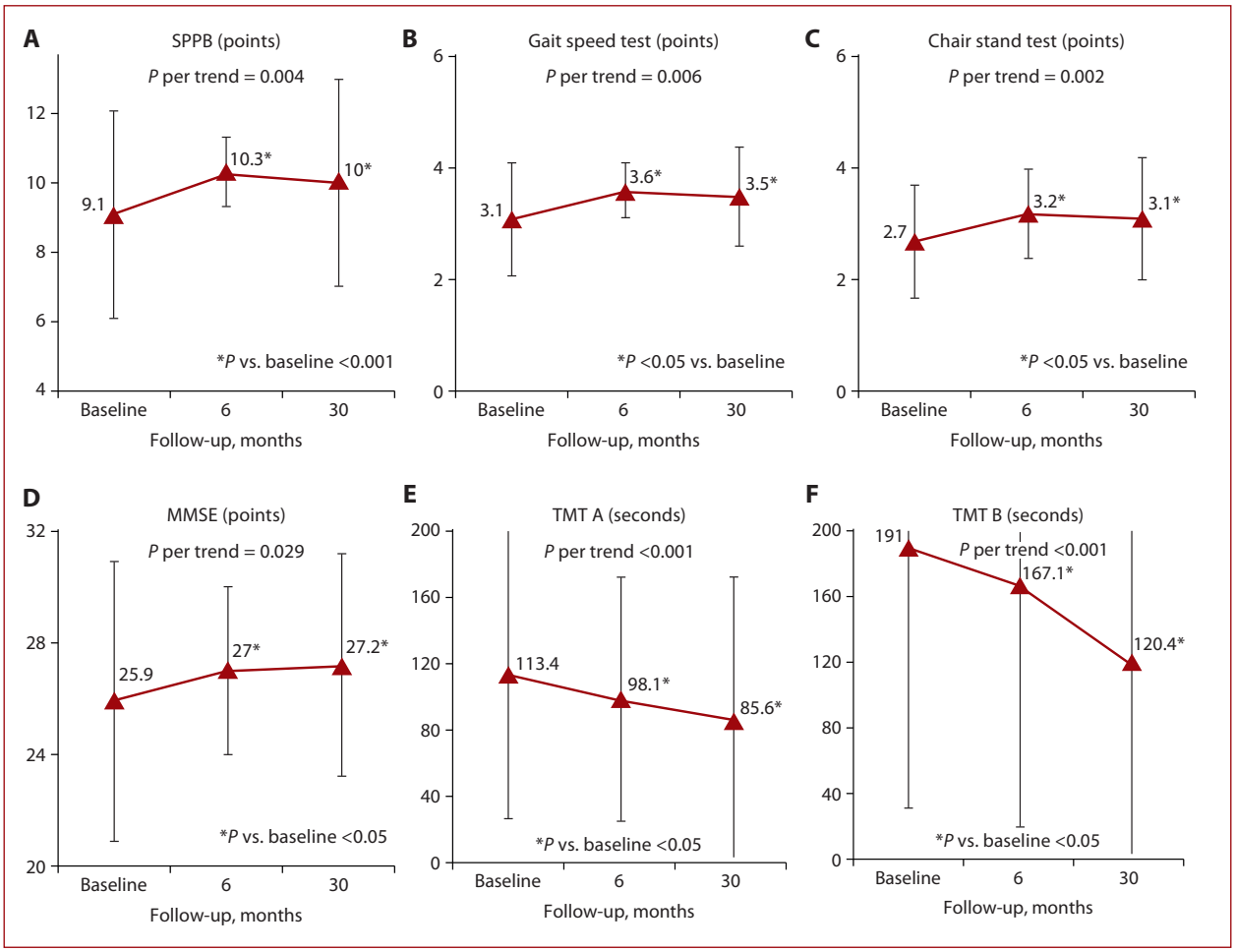

Figure 1. Changes with cardiac resynchronization therapy occurring between baseline and 30-month evaluation of Short Physical Performance Battery (SPPB) total score (**A**), Gait Speed Test (**B**) and Chair Stand Test (**C**), and Mini-Mental State Examination (MMSE) (**D**), Trail Making Test (TMT) A (**E**) and B (**F**). The asterisk indicates a significant difference between each follow-up evaluation and the baseline value

optimized in a real-world scenario, while sodium-glucose co-transporter 2 inhibitors were not clinically available at the time of recruitment. Moreover, we enrolled a small number of patients. To evaluate cognitive function, we used the MMSE. The test is widely used and correlated with the Montreal Cognitive Assessment [15]. Moreover, in the Montreal Cognitive Assessment, the visuospatial/executive task contains a simplified version of the TMT B, which we evaluated in its extended form. Last, our study is hypothesis generating, and its findings should be confirmed by specifically addressed experiences. The relatively small sample size, although managed through parsimonious modelling, may limit the generalizability of the presented estimates. In conclusion, CRT could be an invaluable tool to hinder disability progression in HF patients. Accordingly, current findings highlight the importance of Comprehensive Geriatric Assessment, especially in the routine management of older, complex, and frail subjects.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Acknowledgments: We remember Luigi Padeletti, MD, Professor of Cardiology, a mentor of all of us, great physician, reference and researcher in arrhythmia and electrophysiology. This work was inspired by his sensitivity and passion for medicine.

Conflict of interest: None.

Declaration of artificial intelligence use: Nothing to disclose.

Funding: None.

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