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Cardiac resynchronization therapy improves functional status and cognition☆

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ABSTRACT

Background: Many trials demonstrated the beneficial effects on hospitalizations and mortality of cardiac resynchronization therapy (CRT). The purpose of this study was to evaluate CRT effects on functional performance and cognition, two determinants of disability, frailty development and survival.
Methods: All consecutive patients receiving a CRT device were evaluated at baseline and at the 6-month follow-up. Functional profile was assessed with the Short Physical Performance Battery (SPPB), a measure exploring balance, gait, strength and endurance, highly predictive of incident disability and mortality. The Mini-Mental State Examination (MMSE) was used to study the cognitive profile.
Results: We enrolled 54 patients; two of them died during the follow-up, two refused to continue the study. Age was 67 ± 10 years (men: 80%, LVEF: 28 ± 5%); medical therapy was optimized (ACE-I/ARB: 84%, beta-blockers: 80%). After 6 months, CRT was associated with the improvement of LVEF (35 ± 8 vs. 28 ± 5%, $p < 0.001$) and NYHA Class (1.8 ± 0.6 vs. 2.6 ± 0.5, $p < 0.001$), and with the reduction of left ventricular end-systolic diameter (50 ± 9 vs. 57 ± 9 mm, $p < 0.001$). SPPB improved in its total score (10.3 ± 2.0 vs. 9.1 ± 2.7, $p < 0.001$) and in the scores exploring gait speed and strength and endurance. These changes were associated with a better cognitive profile (MMSE score: 27.0 ± 3.5 vs. 25.9 ± 4.8, $p = 0.009$). Advanced age was an independent predictor of improved functional performance and cognition.
Conclusions: CRT is associated with higher functional and cognitive profile after only 6 months of therapy. These findings let us hypothesize a powerful effect of treatment to slow disability and frailty development in heart failure.

1. Introduction

Current guidelines consider cardiac resynchronization therapy (CRT) a cornerstone for the management of heart failure (HF) [1]. Randomized controlled trials clearly demonstrated that CRT significantly reduces mortality and hospitalizations in subjects with severely depressed left ventricular (LV) ejection fraction (EF) and prolonged QRS duration [2–5]. LV reverse remodeling, EF and NYHA Class improvement are largely independent of age [6]. Recent evidence shows that cognitive decline shares some risk factors with HF [7], and the two conditions act synergistically in the onset of disability, hospitalizations and mortality [7–9]. Pre-frailty - a potentially reversible state, identified by slow gait

Abbreviations: CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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speed, exhaustion and low energy expenditure - is an independent predictor of new cardiovascular events in older adults [10]. Although it has been demonstrated that CRT increases cerebral blood flow in responder patients [11], the only study on the effects of therapy on psychological and neurocognitive endpoints in a HF population found that attention and information processing seemed to improve in a small cohort of patients after a 3-month follow-up [12]. To the best of our knowledge, the association between CRT and measures of physical, cognitive and psychological function has not been studied. The aim of our study was to assess if CRT affects neurocognitive and physical outcomes at 6 months from device implantation.

2. Methods

2.1. Patient selection and evaluation

We prospectively enrolled all consecutive patients undergoing implantation of devices for CRT (CRT-P) or CRT and defibrillation (CRT-D) who met the following criteria: willingness to participate (informed consent obtained in each case); severe reduction of LVEF (≤35%); NYHA Class II–IV after medical therapy optimization; QRS duration ≥120 msec. The relevant institutional review board approved the research protocol which conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Enrollment took place between January and April 2014 in three Italian centers. Each patient received a three pacing-lead device, programmed to obtain the highest proportion of ventricular stimulation (>90% of total beats). All patients underwent a cardiologic evaluation at baseline, before CRT implantation, and at the 6-month follow-up. Responder status was defined as a 15% increase of LVEF and/or by a 15% reduction of LV end-systolic volume. A pre-implantation and a 6-month follow-up battery of tests exploring functional, neurocognitive and psychological profile were administered to all patients. At follow-up, personnel overseeing questionnaires and scales were unaware of the baseline results.

Functional status was assessed by Basic (ADL) [13] and Instrumental Activities of Daily Living (IADL) scales [14], and the Short Physical Performance Battery (SPPB) [15]. ADL describe the need for assistance in bathing, dressing, eating, transferring between the bed and a chair, using the toilet, and continence [13]. IADL describes the need for assistance for cooking, housework, transport, shopping, finances, taking own therapy and using the telephone [14]. The SPPB is a battery of tests used to assess lower extremity function, measuring balance, gait speed, and strength/endurance [15]. To test standing balance, subjects must maintain their feet in the side-by-side, in the semi-tandem and in the tandem positions in consecutive steps of 10 s each. The Gait Speed Test evaluates the time required to walk 4 m at a normal pace. In the chair stand test, participants have to rise five times from a chair as fast as possible without the help of their arms. For each part of SPPB, score ranges from 0 — unable to perform the task, to 4 — optimal performance. A summary measure is created adding the single results (range: 0–12), with higher scores indicating a better functional status. SPPB is able to predict ADL and mobility-related disability at 4 years even in persons not disabled at baseline [15].

Cognitive profile was assessed using the Mini-Mental State Examination (MMSE) [16] and the Trail Making Test (TMT) A and B [17]. MMSE evaluates orientation, registration and recall (memory functions), attention, language and praxis [16]. The total score is 30; results must be corrected by age and education. The cut-off value of <24 is considered clearly abnormal; a score <27 suggests a risk of dementia [16,18]. We studied CRT-associated changes of MMSE in the whole population and in the score groups 27–30 and <27. The TMT A and B are instruments of neuropsychological evaluation [17,19]. To perform TMT A and B, patients receive a picture consisting of 25 circles randomly distributed that must be connected in ascending order. In Part A, exploring visual search and motor speed skills, there are only numbered circles (1–25). In Part B, expressing higher-level cognitive tasks, such as mental flexibility, the circles include both numbers (1–13) and letters (A–L) [19]. Results for both TMT A and B are expressed reporting the time needed to conclude the task, with better performances associated with shorter times [17].

Psychological profile was evaluated using the Profile of Mood States rating scale (POMS) [20,21], the Pittsburgh Sleep Quality Index (PSQI) [22] and the Personal Health Questionnaire Depression Scale (PHQ-8) [23]. The POMS, developed to evaluate transient mood states, consists of 65 adjectives/brief phrases, which are rated on a 5-point Likert scale from 1 - not at all, to 5 - extremely. Grouping the different characteristics, six subscales are identified: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, vigor-activity, and confusion-bewilderment. A seventh score, expressing Total Mood Disturbance, is calculated subtracting the "positive" score of vigor-activity from the sum of the other five subscales [20,21]. The PSQI is a self-rated questionnaire evaluating sleep quality in the preceding month. Nineteen items are grouped to explore the following seven sleep components: subjective quality, latency, duration, habitual efficiency and disturbances, medications and daytime dysfunction. Each component is scored from 0 to 3 and contributes to generate a global score, ranging from 0 to 21. Higher scores indicate a worse sleep quality [22]. The PHQ-8, a tool to diagnose depressive disorders, explores the frequency of eight different conditions (i.e., interest in doing things, sleeping too much, feeling tired, appetite and concentration disturbances, feeling bad about oneself, speaking too slowly or being restless) in the last two weeks, with scores ranging from 0 – not at all, to 3 – nearly every day. A total score ≥10 could be associated to major depression [23].

2.2. Statistical analysis

Data were analyzed with IBM SPSS Statistics (version 22; Armonk, NY, USA). Continuous variables are expressed as mean ± SD or, for wide distributions, as median value (25th–75th percentile). Student's t test or

Table 1
Clinical, instrumental and laboratory characteristics, and drug therapy of patients.

(N = 50)	
Age (years)	67 ± 10
Men [n, (%)]	40 (80%)
Weight (Kg)	81 ± 15
Height (cm)	172 ± 8
Smoke [n, (%)]	21 (42%)
Diabetes Mellitus [n, (%)]	15 (30%)
Dyslipidemia [n, (%)]	21 (42%)
Hypertension [n, (%)]	31 (62%)
Ischemic heart disease [n, (%)]	22 (44%)
NYHA Class [n, (%)] - II	20 (40%)
NYHA Class [n, (%)] - III	30 (60%)
LBBB [n, (%)]	47 (94%)
QRS duration (ms)	154 ± 22
Atrial fibrillation [n, (%)]	11 (22%)
Creatinine concentration (mg/dL)	1.2 ± 0.4
Hemoglobin (g/dL)	13.3 ± 1.9
Sodium (mEq/L)	139 ± 3
Uric Acid (mg/dL)	6.1 ± 2.2
ACE-Inhibitors [n, (%)]	32 (64%)
ARB [n, (%)]	10 (20%)
Beta-blockers [n, (%)]	40 (80%)
Antialdosterone antagonist [n, (%)]	25 (50%)
Digoxin [n, (%)]	5 (10%)
Diuretics [n, (%)]	42 (84%)
Statin [n, (%)]	25 (50%)
Allopurinol [n, (%)]	9 (18%)
Amiodarone [n, (%)]	9 (18%)

Continuous data are presented as mean ± standard deviation, categorical data as counts and percentages; ARB: angiotensin receptor blockers; LBBB: left bundle branch block; LV: left ventricular; NYHA: New York Heart Association.