Cardiac Resynchronization Therapy: A Pilot Study Examining Cognitive Change in Patients Before and After Treatment

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ABSTRACT

Background: Cardiovascular patients with reduced cardiovascular output and capacity such as those with congestive heart failure (CHF) have demonstrated cognitive-related dysfunction. The use of cardiac resynchronization therapy (CRT) is considered standard care for CHF patients who do not improve despite optimal medical therapy. Cardiac resynchronization therapy may improve neurocognitive and psychosocial functioning in patients by increasing cardiac output and cerebral perfusion.

Methods: A total of 20 patients were examined before and 3 months after CRT device implantation, via administration of standard neurocognitive and psychosocial testing measures.

Results: Significant improvements in neurocognitive measures of attention (Digit Span: $t[20] = -2.695$ [$55.94 \pm 9.27 - 62.31 \pm 10.05$], $P = 0.015$) and information processing (Digit Symbol: $t[20] = -4.577$, $P < 0.001$; Controlled Oral Word Association Test: $t[20] = -3.338$, $P = 0.004$) were demonstrated. Improvements in cardiac-specific quality of life were also significant (Minnesota Living with Heart Failure Questionnaire: $t[16] = 3.544$, $P = 0.005$ [$55.17 \pm 18.23 - 36.75 \pm 18.00$]; The Left Ventricular Dysfunction Questionnaire: $t[16] = 3.544$, $P = 0.003$ [$63.43 \pm 23.35 - 43.29 \pm 21.62$]).

Conclusion: These results represent clinically significant, qualitative, and quantitative cognitive functional benefits for patients from a neurocognitive and psychosocial perspective. Results suggest that biventricular pacing improves cardiovascular outcome and psychosocial functioning in patients with CHF. The future investigation of a larger sample would be beneficial in establishing the depth and breadth of this improvement.

Introduction

Congestive heart failure (CHF) is the leading cause of hospitalization and cardiovascular disability in adults in the United States over the age of 65, and is associated with high treatment costs[1] and mortality (~50% at 1 year in the New York Heart Association [NYHA] class IV patients).[2] Approximately 30% of patients with CHF present with significant ventricular dyssynchrony and conduction disturbances[3] consistent with bundle branch block. Cardiac resynchronization therapy (CRT), via biventricular pacing, attempts to improve the mechanical efficiency of the heart by "resynchronizing" ventricular contraction. In multiple clinical trials, CRT has been shown to improve 6-minute hall walk distances, NYHA functional class, quality of life (QOL), ejection fraction (EF), mortality, and time to first hospitalization[4] in CHF patients. Cardiac resynchronization therapy also has a significant and sustained mortality benefit (ie, 40%–51%) as recently reported in the Care-HF trial[5] and previously by meta-analysis.[3] The use of CRT and optimized pharmacotherapy are considered standard care for CHF patients with low EF, wide QRS, and NYHA class III-IV functional status.

The degree of left ventricular dysfunction is also linked to cognitive dysfunction.[6,7] Specifically, mild hypoxia associated with hypoperfusion or reduced blood oxygenation

This study was partially funded by an investigator-initiated grant from Medtronic, Inc. Dr. Vazquez has received speaker honorarium from Medtronic. Dr. Sears serves as a consultant to Medtronic and has or has had research grants from Medtronic and St. Jude Medical and has received speaker honorarium from Medtronic, Boston Scientific, St Jude Medical, and Biotronik. Dr. Conti serves as a consultant to Medtronic and has or has had research grants from Medtronic and St. Jude Medical and has received speaker honorarium from Medtronic, Boston Scientific, and St. Jude Medical.

Clin. Cardiol. 33, 2, 84–88 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20710

Received: July 19, 2009
Accepted with revision: October 20, 2009

is hypothesized to be a mechanism for cognitive deficits in CHF patients, and presents clinically via impaired attention, concentration, and deficits in planning, initiating, and carrying out activities.[8] Additional metabolic disturbances associated with CHF, such as impaired hepatic or renal functioning, result in cognitive dysfunction ranging from transient states of confusion to delirium, and resolve with a return to metabolic homeostasis.[9] Even mild cognitive impairment in the elderly can have significant functional and QOL impacts that can result in disability. However, we are not aware of any data using a pacing/defibrillator group intervention to examine these possible effects. We hypothesized that CRT, by increasing cardiac output and cerebral perfusion, could result in general improvement in cognitive function. To test this hypothesis, the purpose of the current prospective, controlled study was to examine neurocognitive and psychosocial functioning in a preimplant/postimplant sample of CRT patients. Preliminary data from this data set using half the sample (10 patients) were published in the proceedings of the Transactions of the American Clinical and Climatological Association,[10] and suggested improvements in attention and information processing in patients, as well as, psychosocial functioning. The current study extends the sample to a full and final population of 20 patients.

Methods

A total of 20 patients undergoing implantation of a biventricular pacing device for CRT were recruited to participate in this study prior to placement their device (implantable cardioverter defibrillator [ICD] or no ICD). Participants met standard clinical criteria for CRT (EF <35%, a QRS duration ≥130 ms, and NYHA class III-IV). Exclusion criteria included level of education <8th grade, illiteracy, and history of stroke or active dementia (when screened using the Mini Mental Status Exam).[11]

Following informed consent; a doctoral level research associate administered a preimplant baseline neurocognitive battery of tests that included measures of attention, processing speed, declarative memory, and language. Follow-up testing was performed 3 months postimplant using the same neurocognitive battery. Alternate forms of measures known to be susceptible to practice effects were used to ensure accuracy in assessing changes in neurocognitive functioning. Additionally, participants were asked to complete self-report measures of psychosocial functioning, general QOL, and cardiac-specific QOL at both baseline and 3-month follow-up. Repeat echocardiography was performed at the 3-month routine clinical follow-up visit to provide responder/nonresponder classification. The test administrator was blinded to the echocardiographic results throughout the study.

Measures

Attention: Digit span test[12]: Digit Span is a measure of auditory attention capacity and mental manipulation. Strings of number sequences are presented for repetition. When 2 digit strings are correctly repeated, the length of the next pair of digit strings is increased. The digit strings are first to be repeated in the presented sequence and then the digit strings are to be repeated in reverse sequence. Scores are based on the number of digit pairs successfully completed.

Trail making test, parts A and B[13]: The Trail Making Test (TMT) is a timed sensitive measure of visuomotor speed, conceptual tracking, and attention. Part A of the TMT is a test requiring simple numeric sequencing. Part B of the TMT is a more complex task, which requires tracking the concepts and shifting between number and letter sequences, as well as planning motor behavior. Scores are based on time to completion.

Speed of processing: Digit symbol test[12]: Digit Symbol is a sensitive measure of diffuse brain disease affecting attention, visual scanning, and motor output abilities. Subjects are asked to fill in blank spaces below numbers with the correct symbols according to a key of digit-symbol pairs. Scores are based on the number of correct responses provided in a single 120-second trial. Alternate forms were created using the same digits and symbols in different pair combinations.

Declarative memory: Hopkins verbal learning test — revised[14]: The Hopkins Verbal Learning Test (HVLT) assesses auditory learning and memory for a 12-word list presented in 3 separate learning trials. In the first trial, subjects recite all words that can be recalled. In the second trial, patients recite the words they recall after waiting approximately 20 minutes. The final trial is a 24-word recognition trial in which the original 12 target words are imbedded in a group of 24 words.

Language functioning: Controlled oral word association test[15]: The Controlled Oral Word Association Test (COWA) is a sensitive indicator of cognitive deficits associated with brain dysfunction. Subjects are asked to list as many words that begin with a specified letter as they can in three 60-second trials. Scores are based on the number of words generated.

Psychosocial adjustment and quality of life: Center for epidemiologic studies depression scale[16]: The Center for Epidemiologic Studies Depression Scale (CES-D) is a well-known, widely used instrument assessing various levels of depressive symptomatology with high validity and reliability in patient samples. Respondents indicate how frequently they experienced each symptom in the past week. Total scores range from 0 to 60 and reflect the number of depressive symptoms and duration; higher scores indicate higher levels of depression. A standard cut-off of 16 indicates clinically significant symptoms of depression. Previous research has demonstrated that the CES-D is

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20710

Table 1. Study Measures of Cognition, Psychological Functioning, and Quality of Life

Domain	Measure	n	Mean Preimplant	Mean Postimplant	*P* Value
Attention	Digit Span	20	55.94	62.31	0.015[a]
Attention	TMT Part A	20	44.77	45.38	0.834
Speed of Processing	Digit Symbol	20	46.57	54.73	<0.001[a]
Executive Function	TMT Part B	20	46.61	48.94	0.172
Language	COWA	20	47.05	51.72	0.004[a]
Depression	CES-D	16	14.25	12.75	0.313
Quality of Life Cardiac Specific	MLHFQ	16	55.17	36.75	0.005[a]
Quality of Life	LVD-36	16	43.29	63.43	0.003[a]
Trait Anxiety	STAI	16	36.50	34.75	0.544

All cognitive test scores represent age and education converted T-scores.
[a] Indicates statistical significance.

highly sensitive and specific with a high internal reliability coefficient of 0.85.[16]

Minnesota living with heart failure questionnaire[17]: Cardiac-specific QOL has often been assessed with the use of the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The MLHFQ has demonstrated adequate psychometric properties and responsiveness in clinical trials. On the MLHFQ, respondents complete a series of questions asking how frequently their CHF has affected their life in the past month.

The left ventricular dysfunction questionnaire[18]: The Left Ventricular Dysfunction Questionnaire (LVD-36) is a cardiac-specific measure designed to assess the impact of left ventricular dysfunction on daily life and well-being. Responses are dichotomous (true or false). True responses are summed, then calculated as a percentage; higher scores indicate worse functioning (ie, 0 = best possible score).

State-Trait Anxiety Inventory[19]: The State-Trait Anxiety Inventory (STAI) is a 40-item self-report questionnaire designed to measure both state and trait anxiety. Trait anxiety is defined as a relatively enduring personality characteristic, or more specifically, as anxiety proneness. State anxiety is defined by a short-lived anxiety, usually induced by an event or circumstance. The internal reliability of both the state and trait anxiety scales has been shown to be uniformly high across samples of adults ranging from 0.89 to 0.96.[19]

Statistical Analyses

Paired *t* tests were performed to examine changes in cognitive and psychosocial functioning before and after biventricular pacing. Patients were used as their own controls. Prior to conducting analyses, raw scores on measures of cognition were converted to T-scores, utilizing a standardization process that adjusts for age and education effects. This is a normative adjustment made in neuropsychological literature to aid in comparison of disparate groups.[9]

Results

A total of 20 patients completed pre and post measures of neurocognitive and psychosocial functioning, via completion of a 1-hour neurocognitive and self-report battery at Shands Hospital at the University of Florida. The sample mean age was 54.8 ± 11.94 years, and consisted predominantly of white males (87%). Mean EF prior to CRT was 17.5% ± 13%. The baseline pre-CRT sample included 15% of patients at NYHA class II, 60% at class III, and 25% at class IV status. At 3-month follow-up, post-CRT mean EF improved to 30% ± 10% over baseline ($P < 0.001$). Functional status also improved with CRT. The sample also demonstrated general improvement in NYHA status with 15% at NYHA class I, 70% at class II, 10% at class III, and 0.5% at class IV at the 3-month follow-up time point. Remarkably, all patients were responders to CRT and no patients received ICD shocks throughout the course of the study.

Significant improvements were observed in attentional processing 3-months post-CRT (Digit Span: $t[20] = -2.695$ [55.94 ± 9.27–62.31 ± 10.05], $P = 0.015$) when compared to baseline. Significant improvements were also observed in processing speed (Digit Symbol: $t[20] = -4.577$, $P < 0.001$; COWA: $t[20] = -3.338$, $P = 0.004$) at 3-months post-CRT. Specifically, the average T-score for Digit Symbol increased from 46.57 ± 10.19 to 54.52 ± 9.08 and for COWA from 47.05 ± 8.50 to 51.72 ± 7.76. No significant

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20710

cognitive changes were seen on TMT Part A ($t[20] = -0.213$, $P = 0.834$) or TMT Part B ($t[20] = -1.425$, $P = 0.172$).

Cardiac-specific QOL also improved after 3 months of CRT therapy, as measured by the MLHFQ ($t[16] = 3.544$, $P = 0.005$ [55.17 ± 18.23–36.75 ± 18.00]) and the LVD-36 ($t[16] = 3.544$, $P = 0.003$ [63.43 ± 23.35–43.29 ± 21.62]). There were no significant changes in depression (CES-D: $P = 0.313$) or anxiety (STAI: $P = 0.544$) as our sample did not meet clinical criteria for depression or anxiety at baseline or at 3-month follow-up.

Discussion

The current study demonstrates that cognitive functioning associated with chronic CHF appears to be significantly improved in patients responding to CRT, specifically in the domains of attention, working memory, and speed of processing. Additionally, cardiac-specific QOL was significantly improved at 3 months postimplantation, suggesting that both cognitive and psychosocial health is aided by resynchronization therapy in CHF patients.

Cognitive decline amongst cardiovascular populations was initially established in large-scale epidemiological studies,[20] that demonstrated attention and processing speed are affected by decreased cerebral perfusion and atherosclerotic changes. In a recent study, Vogels et al[21] found that the pattern of cognitive impairment in CHF populations include primarily memory, attention, speed of processing, and language deficits. The frontal cortex and orbitofrontal regions, which subserve a variety of functions including attention and processing speed, may be particularly affected by the hypoperfusion often seen in CHF populations.[22] Braunwald suggests that the burden of CHF and its accompanying cognitive sequelae will only increase in the future, as the treatment and prognosis of CHF continues to improve.[23] In the current study, a sample of CHF patients receiving CRT benefited from biventricular pacing across the specific domains of attention and concentration.

The current study has some specific limitations to consider when interpreting the results. First, this study is best considered a pilot study to examine whether a large-scale trial focused on cognition in CRT patients is reasonable. The small sample size and its resulting lack of diversity limits our ability to conclude definitely, but the current evidence suggests that further examination of neuropsychological testing in CRT research in a larger, more representative population is viable. Additional attention to markers of CRT response, including classification of responders vs nonresponders, as well as degree of dyssynchrony, may also provide further information that identifies characteristics most closely associated with the cognitive benefit of CRT. The current study sample generally showed a robust response to CRT on echo parameters and larger sample sizes would allow for closer examination of the relationship of the cognition-response continuum. Lastly, although there was no control arm, the patients served as their own controls.

Conclusions

Results of this pilot study suggest that CRT improves cognition and cardiac-specific QOL within 3 months of treatment. Commensurate with known functional changes that occur with increased cerebral perfusion to frontal domains, this sample of CRT responders showed improvements in tasks of attention, working memory, and processing speed. Heart failure patients who often report memory complaints to their physicians may be experiencing attentional/organizational problems, rather than frank changes in memory. Given that patient education efforts are dependent on attention and organizational capacity, it is critical to include spouses and family members, and repeat information before device implantation as well as at follow-up appointments, in addition to providing information in written format (eg, handouts). Cardiac resynchronization therapy is valuable for not only the improvement of cardiovascular health, but also across the domains of QOL and neuropsychological functioning.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20710

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20710