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Link Between Change in Cognition and Left Ventricular Function following Cardiac Resynchronization Therapy

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Abstract

PURPOSE—In patients with heart failure, reduced cardiac ejection fraction has been associated with impaired cognition. Improving cardiac function may have beneficial effects on cognition; however, no controlled intervention studies have examined this possibility. Cardiac resynchronization therapy (CRT) is 1 intervention that has been shown to increase cardiac function. The goals of the current study were to: 1) evaluate neuropsychological performance before and 3-months after CRT and 2) examine follow-up neuropsychological performance of patients classified based on extent of improved left ventricular ejection fraction (LVEF).

METHODS—Twenty-seven patients with moderate to severe heart failure completed a neuropsychological assessment, 6-minute walk test, and transthoracic echocardiogram prior to and 3-months post-CRT. Patients were classified based on improvement in LVEF. Results of a MANOVA revealed a significant effect of improvement in LVEF on change in cognition (Wilk's lambda, $P=.031$).

RESULTS—Patients with improved LVEF demonstrated significant increases on measures of executive functioning ($F=8.57$, $P=.007$) and visuospatial function ($F=7.52$, $P=.011$) and less decline on global cognition ($F=5.73$, $P=.024$) than those without LVEF improvement.

CONCLUSIONS—Findings provide preliminary evidence that improved LVEF in response to CRT is associated with enhanced cognitive outcomes within 3 months of CRT. Patients with improved LVEF showed better outcomes on measures of executive functioning, global cognition, and visuospatial functioning. Future controlled large scale trials will be necessary to determine whether there is an underlying causal relationship linking increase in LVEF and cognition.

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Keywords

Heart failure; Cardiac resynchronization therapy; Cognition; Neuropsychology; Left ventricular ejection fraction

A number of studies have found that cognitive impairments are common in patients with heart failure with prevalence estimates ranging from 25-75% depending upon the sample.¹ In patients with systolic dysfunction, cognitive deficits are most pronounced in higher order executive functioning, attention, learning, recall, and reaction time.¹ There is evidence that these cognitive deficits negatively impact activities of daily living² and increase risk of mortality above and beyond the presence of heart failure alone.³

Research on the etiology of cognitive impairment in heart failure has focused on chronic circulatory insufficiency. Reduced cardiac output and/or ejection fraction have been associated with alterations in white matter in the brain observed on neuroimaging⁴⁻⁶ and with diminished neuropsychological test performance.^{7,8} Our lab has shown that reduced cardiac output is associated with deficits in higher order executive functioning among stable geriatric outpatients with a range of cardiovascular diseases.⁷ These higher order cognitive skills include cognitive flexibility, initiation and maintenance of effort, fluency, and working memory. The typical profile of executive dysfunction observed among patients with cardiovascular disease may be associated, at least in part, with reduced blood flow to vulnerable subcortical regions in the brain.⁹ We have also shown that among patients with more advanced heart failure, reduced left ventricular ejection fraction (LVEF) is associated with a wider range of cognitive deficits including global cognition, attention, working memory, fluency, and delayed memory⁸ suggesting that the relationship between LVEF and cognition involves more global effects for patients with the most severely impaired cardiac function.

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure and electromechanical dyssynchrony who demonstrate persistent functional limitations despite optimized pharmacologic treatment. CRT is associated with improvements on various measures of cardiac structure and function, health status, and quality of life.¹⁰⁻¹² Only 1 previous, uncontrolled study of 10 patients has examined its effects on cognitive function.¹³ Given that two-thirds of patients experience improved cardiac function and symptoms following CRT, and that there is an association between left ventricular systolic dysfunction and cognitive impairment, CRT is an ideal intervention to test the association between cardiac function and cognition. The goal of the current study was to examine the relationship between change in LVEF following CRT and cognition during a 3-month follow-up using comprehensive neuropsychological assessment. We hypothesized those patients who experienced improved LVEF after CRT would show associated improvement in executive functioning.

METHODS

Participants were recruited through the heart failure and electrophysiology clinics in a large university teaching hospital. CRT candidates had NYHA Class >II heart failure, LVEF <35%, and QRS duration >130ms at the time of the initial clinical intake visit and scheduling of CRT. Study inclusion criteria required that participants were age 55 or older, English speaking with at least an 8th grade education, and normal or corrected hearing and vision at the time of the assessment. Participants were excluded if they had a neurological condition, eg, stroke, epilepsy, head injury with loss of consciousness >30 minutes, major psychiatric disorder, eg, schizophrenia, bipolar disorder, current untreated major depression, or anxiety disorder, or a previous diagnosis of dementia.

Study Procedures

The study was approved by the local Institutional Review Board and all patients provided written informed consent prior to participation. Participants completed a baseline study visit within the 2 weeks before CRT and a follow-up study visit approximately 3 months postCRT. The average length of follow-up evaluation after CRT was 91 days (SD=13). Twenty-six patients received a biventricular (BiV) pacemaker with implantable cardioverter defibrillator (ICD) and 1 patient received a BiV pacemaker without a defibrillator. During the baseline study visit participants completed a medical history interview, neuropsychological test battery, and cardiovascular measures, ie, electrocardiogram, echocardiogram, and 6-minute walk.¹⁴ Medical history variables were coded according to participant self-report and were confirmed by a medical chart review. The follow-up visit included neuropsychological assessment, echocardiogram, and 6-minute walk test (6MWT). The decision to assess patients after 3 months was based upon previous literature suggesting that improvement in cardiac functioning measures,¹⁵ quality of life,¹⁶ and cognition¹³ occurs by 3 months. The 3 month follow-up was chosen to provide sufficient time to observe cardiac and cognitive change, while simultaneously minimizing the potential of unrelated adverse health events and maximizing retention.

BiV/ICD Implantation

BiV/ICD implantation was performed by staff electrophysiologists as a part of their routine clinical practice. All patients signed informed consent for the clinical device implant in addition to the study consent. Right atrial and right ventricular leads were placed via cephalic or axillary vein puncture. The left ventricular lead delivery system was placed via axillary vein puncture and advanced into the coronary sinus. Left ventricular leads were placed in the lateral branches of the coronary sinus. Biventricular pacing programming was carried out at the discretion of the clinical team. Formal echo AV optimization was not performed.

Measures

Cardiovascular Assessment

Echocardiogram: Transthoracic 2-D echocardiograms were performed with an IE33 machine (Philips, Andover, MA) according to American Society of Echocardiography standards. LVEF was calculated based upon modified Simpson's biplane method of discs¹⁷ with the sonographer blinded to patient clinical status. In 3 participants, a single plane method from the apical 4-chamber view was employed due to suboptimal image quality.

6MWT: The 6MWT has been widely used to measure the response to interventions in pulmonary and cardiac disease and was administered according to American Thoracic Society guidelines.¹⁴

Psychosocial Assessment

Minnesota Living with Heart Failure Questionnaire (LHFQ)¹⁸: The LHFQ is a 21-item self-report measure of heart failure related quality of life.¹⁹

Beck Depression Inventory-II (BDI-II)²⁰: The BDI-II is a 21-item self-report questionnaire measuring severity of depressive symptoms. The maximum score is 63, with scores greater than 14 suggesting clinically significant depressive symptoms.

Neuropsychological Assessment

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)²¹: This 20-30 minute battery provides an overall measure of global cognition and 5 specific domain

scores (Immediate Memory, Visuospatial/Constructional, Language, Attention, Delayed Memory). It is designed for repeated cognitive assessment.²¹ Alternate forms were counterbalanced at study entry and follow-up to minimize test re-test and order effects.

Three additional measures of executive functioning, ie, sequencing, verbal fluency, and working memory, were included, as the executive functioning domain of cognitive functioning is often affected in patients with cardiovascular disease and is not comprehensively assessed on the RBANS.

Trail Making Test Parts A and B (TMT)²²: TMT Part B was included in the final analysis as it assesses psychomotor processing speed, sequencing, and cognitive flexibility.

Controlled Oral Word Association (COWA)²³: This verbal fluency task assesses the ability to initiate and maintain effort and requires the subject to rapidly produce words beginning with specified letters.

WAIS-III Letter-Number Sequencing²⁴: This test of working memory requires the subject to listen to a series of randomly arranged numbers and letters, eg, F-4-L-7-Q-2, and repeat the series starting with the numbers (lowest to highest) and then the letters (in alphabetical order).

Data Analysis

Data were analyzed using SPSS 17.0 computer software (SPSS Inc., Chicago, IL).

Classification of LVEF Change—Patients were classified based on their percent improvement in LVEF on echocardiogram from baseline to follow-up. Based on the previous clinical trials literature,²⁵⁻²⁷ the cut point was set at $\geq 15\%$ improvement in LVEF at 3-month follow-up. Participants were classified as experiencing LVEF improvement if they had $\geq 15\%$ increase in LVEF. In contrast, participants were classified as having minimal LVEF change if they had $< 15\%$ improvement and/or experienced a major complication following CRT such as lead displacement.

Calculating Cognitive Domain Scores—Seven cognitive domain scores were calculated. Six of the 7 domain scores were derived from the RBANS²¹, ie, global cognition, immediate memory, delayed memory, language, visuospatial skills, and attention. The seventh, executive functioning domain score, was calculated by averaging the standard scores of the 3 executive functioning tests, ie, Trail Making Test Part B,²⁸ Letter-Number Sequencing,²⁴ COWA.²⁹ Thus, the executive functioning domain reflects initiation and maintenance of effort, processing speed, cognitive flexibility, and working memory.

Consistent with established procedures for scoring neuropsychological tests, raw cognitive test scores for each participant were converted into standard scores (mean=100, SD=15) compared to age-corrected normative data. Lower standard scores are indicative of worse cognitive performance, ie, a standard score of 85 reflects performance that is 1 SD below the mean compared to expectations for the individual age).

Statistical Methods—A series of independent groups *t*-tests and *Chi-square* analyses were calculated to compare the demographic and medical background of those participants who experienced LVEF improvement versus minimal LVEF change. We first compared 6-minute walk, QRS duration, LVEF, left ventricular diastolic volume (LVEDV), left ventricular systolic volume (LVESV), subjective symptoms (LHFQ), depressive symptoms, and the cognitive performance of all participants (N=27) at baseline and follow-up using *t*-tests to identify potential changes for the total sample (Table 2). We also conducted *t*-tests comparing change

in the variables listed above between the LVEF response groups. To correct for multiple comparisons of intercorrelated measures, we applied Sidak's adjustment and reduced the P value to .018 for this series of comparisons.³⁰

To examine the primary aim, the change in cognitive performance from baseline to follow-up was compared for the 2 LVEF groups using a Repeated Measures Multivariate Analysis of Variance (MANOVA). All cognitive domains were entered into the analysis simultaneously in order to minimize multiple comparisons and preserve the 5% Type 1 error rate. LVEF change group was entered as the between-subjects variable and the 7 cognitive domain standard scores were entered as dependent variables. Since the standardized cognitive scores were already corrected for age using normative data, we did not include age as a covariate.

RESULTS

Descriptive statistics regarding the sample demographic and medical characteristics are presented in Table 1. Sixty-three percent ($n=17$) of the sample experienced $\geq 15\%$ improvement in LVEF and 37% did not ($n=10$; 2 of those without improved LVEF experienced lead displacement requiring repeat intervention). There were no significant differences in demographics, medication use, or medical comorbidities at baseline between the LVEF change groups (Table 1). However, patients who experienced $\geq 15\%$ improvement in LVEF had a lower LVEF on the baseline echocardiogram (Table 2). Although all patient LVEF were below 35% on a clinical echocardiogram or angiogram obtained prior to their office visit and scheduling of CRT, some patient LVEF were above 35% on the baseline research echocardiogram which was blinded, quantitative, and obtained within the 2 weeks prior to CRT.

For the total sample, there were significant improvements pre- to postCRT in LVEF (31.5% versus 40.4%, $P<.001$), QRS duration (164.8 msec versus 143.6 msec, $P<.001$), 6MWT (1108.2ft. versus 1203.9ft., $P=.008$), LVESV (113.2mL vs. 85.10mL, $P<.001$), LVEDV (161.05mL vs. 129.81mL, $p<.001$), and LHFQ (31.3 versus 21.6, $P<.05$) (Table 2). There was a non-significant change in depressive symptoms; however, the sample had minimal depression at baseline by design given criteria to exclude individuals with psychiatric comorbidities.

The cognitive performance of the sample fell in the average range, eg, Mean Global Cognitive Standard Score= 94.22; Table 3). No significant improvements in cognition were observed following CRT when all patients were considered together. In contrast, the average standard score on the language domain declined from baseline to follow-up (101.2 to 95.2, $P=.018$).

The results of a repeated measures MANOVA revealed a significant effect of change in LVEF on change in overall cognition (Wilk's $\lambda=0.48$, $P=.031$; Table 3) when all neuropsychological domains were entered into the analysis together. When each individual neuropsychological domain was examined separately, significant positive effects from improved LVEF were noted in three specific cognitive domains. Those with LVEF improvement demonstrated some increase in executive functioning, ie, standard score of 88.92 to 92.71) whereas participants with minimal LVEF change demonstrated some decline in executive functioning during the follow-up period (standard score of 95.89 vs. 93.87) ($F=8.57$, $P=.007$). Those with LVEF improvement showed a minor increase in visuospatial function ($F=7.52$, $P=.011$) and less decline in global cognition ($F=5.73$, $P=.024$) and than participants with minimal LVEF response (see Table 3).

DISCUSSION

Findings from the current study provide preliminary evidence that heart failure patients who experienced improved LVEF after CRT demonstrated more favorable cognitive performance at 3 months. Patients with $\geq 15\%$ improvement in LVEF showed enhanced executive

functioning and visuospatial function, and less decline on global cognition as compared to those with no or minimal LVEF change. These data extend the 1 previously published study of 10 patients that examined changes in cognitive test performance following CRT.¹³ Conti and Sears¹³ observed improvements on measures of attention and processing speed, ie, Digit Span and Symbol Digit, but not delayed memory, ie, Hopkins Verbal Learning Test, 3 months after CRT. Importantly, all of their participants responded to CRT and the authors did not examine change in cardiac function following implantation. Our study included a more comprehensive neuropsychological assessment battery and both patients who experienced improvement in CRT and those that did not. These findings suggest that in addition to primary clinical outcomes of cardiac structure and function and exercise capacity, change in cognition is a novel and important clinical endpoint to be assessed. Furthermore, improved ejection fraction may be one underlying mechanism of change in cognition following CRT.

Classification Based on Change in LVEF

Based on the previous literature on cardiac outcomes following CRT,²⁵⁻²⁷ we classified patients as experiencing a significant improvement in LVEF if their LVEF increased by $\geq 15\%$ of their baseline ejection fraction. Our observation that 63% of our participants experienced LVEF improvement based on this definition is consistent with most other studies.²⁵ Those with LVEF improvement and those without did not differ on any demographic or clinical variables at baseline other than baseline, quantitative ejection fraction. The definition of CRT response has varied between studies and included measures of reverse remodeling, exercise capacity, and change in self-reported symptoms. We chose to define response as narrowly as possible by focusing on the endpoint of LVEF because this measure of cardiac performance has been associated with cognition in cross sectional studies of patients with heart failure.⁸ Furthermore, Yu et al³¹ has shown that improvement in LVEF and reverse remodeling by reduction in LVESV were predictive of cardiovascular morbidity and mortality. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after CRT.³¹ Based on this, we hypothesized that change in LVEF may be an underlying mechanism impacting cognition after CRT.

Pattern of Cognitive Change

We hypothesized that patients who responded to CRT with improved LVEF would demonstrate significant cognitive improvement in the domain of executive functioning. This assumption was based on our previous evidence that systemic hypoperfusion (as measured by ejection fraction and cardiac output) is associated with deficits in executive functioning.^{7, 8} The overarching model of vascular cognitive impairment suggests that the pronounced executive dysfunction observed among patients with cardiovascular disease may be associated with reduced blood flow to vulnerable subcortical regions in the brain, eg, white matter, which are necessary for intact executive functioning.

In the current study of 27 heart failure patients, we observed better cognitive outcomes in executive functioning, global cognition, and visuospatial function among patients with improved LVEF after CRT. The favorable cognitive outcomes were somewhat broader than anticipated. The strongest effects were observed in executive functioning, providing some support for the hypothesized effects by cognitive domain. The difference in cognitive change between the groups was approximately one-half of one standard deviation. This effect over 3 months is modest, but it highlights the possibility of larger differences with a longer follow-up. Future studies will benefit from including measures of daily functioning and treatment adherence to clarify the clinical significance of these cognitive changes.

Study Design Considerations

The study had several limitations that warrant discussion. The sample size was small and the study did not employ a randomized controlled intervention design. We measured change in cognition and cardiac function in patients undergoing CRT in a clinical setting. Future studies including comprehensive cognitive assessment will be necessary to control for intervention vs. no intervention status. Nonetheless, our inherent comparison of patients classified based on change in LVEF did enable us to compare patients that reached a clinically accepted threshold of response to those that did not.

Given the focus on understanding the link between change in ejection fraction after CRT and cognition, we designed the study to have strict exclusion criteria, eg, no history of neurological disease, severe psychiatric condition, or comorbid medical conditions such as kidney disease. These criteria inherently resulted in the inclusion of participants with relatively few comorbidities. One could argue that this approach reduces generalizability to patients with more severe heart failure and medical comorbidities. However, the specificity of our sample is also a significant strength because it simultaneously improved our ability focus on the association between change in LVEF after CRT and cognition with fewer confounds.

Although we designed the study to reduce comorbidities that could affect cognition, the etiology of cognitive impairment in patients with heart failure is multifactorial and we cannot rule out that mechanisms other than change in LVEF contributed to more favorable cognitive outcomes among some patients following CRT. There may be other factors that affect response to CRT, which also affect cognitive function, eg, ischemic vs. nonischemic etiology, medication use.

Summary

In summary, we present the largest body of evidence to date that patients who responded to CRT for heart failure with improved LVEF had better outcomes on measures of executive functioning, global cognition, and visuospatial skills 3-months after CRT. These findings extend the past literature by examining change in multiple domains of cognition and by examining patients with significantly improved LVEF and those with no or little LVEF change, who acted as an inherent comparison group. Our data suggest a link between improvement in cognition and improvement in systemic perfusion. It may be important to clinically monitor patients with poor echocardiographic response for further cognitive decline and conversely, improvement in cognitive function may be a measureable benefit of CRT in addition to improved physical function in heart failure patients. Future large scale studies will be necessary to confirm whether there is an underlying causal relationship linking change in LVEF and cognition.

Condensed Abstract

The study goal was to examine neuropsychological performance before and 3-months after cardiac resynchronization therapy (CRT). Patients (N=27) with moderate to severe heart failure were evaluated. Findings provide evidence that improved left ventricular function in response to CRT is associated with enhanced cognitive outcomes within 3 months of CRT.

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TABLE 1
DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE^a

Patient Characteristics	Total Sample (n=27)		LVEF Improvement (n=17)		LVEF Minimal Change (n=10)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, y	68.4 (9.0)		68.5 (8.2)		68.4 (10.6)	
Gender, female		30%		29%		30%
Education, y	12.2 (3.3)		11.6 (3.6)		13.3 (2.5)	
Systolic BP, mmHg	129.0 (15.4)		133.1 (13.5)		122.0 (15.9)	
Diastolic BP, mmHg	74.1 (9.4)		76.6 (9.3)		69.8 (8.1)	
Hypertension		76%		69%		89%
Hypercholesterolemia		68%		81%		44%
Type 2 diabetes mellitus		41%		47%		30%
Coronary artery disease		44%		41%		50%
History of smoking		67%		71%		60%
History of CABG		11%		7%		17%
Heart failure etiology						
Ischemic		44%		47%		40%
Nonischemic		56%		53%		60%
Medications						
Aspirin		59.3%		64.7%		50.0%
ACE inhibitor		74.1%		76.5%		70.0%
Angiotensin receptor blocker		29.6%		29.4%		30%
Beta blocker		96.3%		94.1%		100%
Statin		66.7%		73.3%		58.3%

^a Responders and non-responders were compared on all demographic and medical variables above using either t-tests for continuous variables or χ^2 analyses for dichotomous variables. None of the comparisons were statistically significant.

Abbreviations: LVEF, left ventricular ejection fraction; BP, blood pressure; CABG, coronary bypass grafting

TABLE 2

CLINICAL MEASURES AT BASELINE AND 3-MONTH FOLLOW-UP

Measure	Total Sample (N=27)		LVEF Improvement (n=17)		LVEF Minimal Change (n=10)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
LVEF, %	31.38***	40.42***	27.53***	40.59***	37.30***	40.11***
LVESV, mL	113.20***	85.10***	136.38	63.67	90.22	59.75
LVEDV, mL	161.05***	129.81***	178.21	104.89	143.00	103.88
QRS duration, ms	163.27***	143.42***	162.80	145.94	163.70	139.40
6-minute walk, ft	1108.18**	1203.86**	1138.21	1220.77	1070.56	1179.44
LHFQ score	31.25*	21.58*	30.33	24.27	34.10	17.11
BDI-II score	7.42	5.65	7.24	6.29	7.70	4.44

Abbreviations: LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume; LHFQ, Minnesota Living with Heart Failure Questionnaire; BDI-II, Beck Depression Inventory-II

* $P < .05$
 ** $P < .01$
 *** $P < .001$

TABLE 3
COGNITIVE DOMAIN STANDARD SCORES AT BASELINE AND 3-MONTH FOLLOW-UP^a

Cognitive Domain Scores	Total Sample (N=27)		LVEF Improvement (n=17)		LVEF Minimal Change (n=10)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Global cognition	94.22	91.04	89.24*	88.71*	102.70*	95.00*
Immediate memory	92.67	91.19	88.76	89.24	99.30	94.50
Delayed memory	95.11	92.00	91.53	87.71	101.20	99.30
Language	101.19*	95.19*	97.94	95.06	106.70	95.40
Visuospatial skills	98.22	95.30	94.53*	95.59*	104.50*	93.10*
Attention	92.00	94.37	88.24	90.94	98.40	100.20
Executive functioning	91.51	93.14	88.92**	92.71**	95.89**	93.87**

^aNeuropsychological standard scores (mean=100, SD=15) were derived using age-corrected normative data as cited in the text. Lower scores indicate worse cognitive performance for all measures.

* $P<.05$

** $P<.01$

*** $P<.001$

LVEF, left ventricular ejection fraction