Treatment with enhanced external counterpulsation improves cognitive functions in chronic heart failure patients

Güçlendirilmiş eksternal kontrpulsasyon tedavisi kronik kalp yetersizliği olan hastalarda kognitif fonksiyonları iyileştirir

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ABSTRACT

Objectives: Chronic heart failure (CHF) has been associated with an increased risk of poorer cognitive performance in older adults. Reversibility of cognitive impairment after medical treatment has been reported, although the restorative effects of enhanced external counterpulsation (EECP) on cognitive performance have not been studied. We investigated the effect of EECP on cognitive functions in CHF patients.

Study design: Thirty-six individuals (mean age: 66±8 years) who were diagnosed with CHF and were New York Heart Association (NYHA) Class II-III and Canadian Cardiovascular Society (CCS) Class II-III participated in this study. Neuropsychological assessment was performed in these patients.

Results: Patients in the EECP treatment group showed a statistically significant improvement in spontaneous naming (p=0.011) and forward row score of the attention subset among domains of cognition (p=0.020) and interference time of executive function (p=0.012).

Conclusion: Enhanced external counter pulsation resulted in improvement in all domains of cognitive functions except verbal and visual memory tests.

ÖZET

Amaç: Kronik kalp yetersizliği (KKY) yaşlı bireylerde kognitif performansın kötüleşme riskinde artma ile ilişkili bulunmuştur. Tıbbi tedavi ile kognitif kötüleşmenin düzeldiği bildirilmiştir. Fakat güçlendirilmiş eksternal kontrpulsasyon'un (EECP) kognitif fonksiyonlar üzerine olan onarıcı etkisi henüz araştırılmamıştır. Biz EECP tedavisinin KKY'li hastaların kognitif fonksiyonları üzerine olan etkisini araştırdık.

Çalışma planı: New York Kalp Birliği (NYHA) fonksiyonel sınıflaması II-III ve Kanada Kardiyovasküler Birliği (CCS) sınıflaması II-III olan, KKY'li 36 hasta (ortalama yaş 66±8 yıl) çalışmaya alındı. Bu hastalarda nörofizyolojik değerlendirmeler yapıldı.

Bulgular: Güçlendirilmiş eksternal kontrpulsasyon yapılan hastalarda spontan adlandırmada (p=0.011), dikkat kavramanın araştırıldığı ileri row skorunda (p=0.020), yönetimsel fonksiyonun karışma zamanında (p=0.012) istatistiksel olarak anlamlı iyileşme olduğu gözlendi.

Sonuç: Güçlendirilmiş eksternal kontrpulsasyon görsel ve sözlü hafıza testleri haricinde kognitif fonksiyonun tüm alanlarında anlamlı iyileşme sağlamıştır.

Despite improvements in medical therapies, chronic heart failure (CHF) is one of the most common cardiovascular disorders and is associated with high morbidity and mortality.[1] Cognitive impairment is prevalent in CHF patients,[2-5] with up to approximately 80% of CHF patients having some form of cognitive impairment.[4] Deficits in attention, executive function and memory are common in heart

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failure patients.[4,5] For example, executive function is a commonly impaired domain and encompasses the brain functions that allow individuals to process information and make decisions related to managing novel situations. Impairments in executive function cause decreases in functional status and self-management ability.[6,7] When CHF patients have worsening symptoms, intact executive function supports accurate processing of the worsening symptoms and concludes that contacts with health care providers are necessary.

In patients with CHF, it is important to teach patients self-care behaviors for preventing fatal events.[8] Impairments in cognitive functions probably contribute to a reduced capacity to understand and comply with treatment regimens, resulting in a worse prognosis.[4]

There are many pathophysiological factors that have been demonstrated to influence the degree of cognitive impairment in CHF, including structural brain pathology, decreased cerebral blood flow, and dysfunction of the autonomic nervous system (ANS).[9,10] CHF patients may have many brain abnormalities on neuroimaging studies, such as cerebral atrophy and infarcts,[11,12] white matter hyperintensities,[13,14] and alterations in cerebral metabolism.[15] Such abnormalities have been strongly associated with cognitive impairment in persons with cardiovascular disease.[16] CHF patients also have reduced cerebral perfusion compared with healthy controls. Decreased cerebral perfusion contributes to cognitive impairment and may be caused by multiple factors.[9]

Despite optimal medical treatments and new revascularization techniques, a significant number of CHF patients have many difficulties in their daily life. Enhanced external counter pulsation (EECP) is a non-pharmacological and non-invasive treatment, administered in an outpatient setting. A course of EECP treatment typically involves 35 one-hour sessions, usually five days a week over a seven-week period. Numerous clinical trials have shown that EECP is safe and effective in patients with ischemic heart disease, with or without left ventricular dysfunction, improving their quality of life. EECP appears to be beneficial as an adjunctive therapy in heart failure patients of any etiology.[17-20]

The present study examines the possibility that cognitive function may be modifiable by EECP treatment by assessing cognitive function over a seven-week period in CHF patients. Evidence of global cognitive improvement was shown in CHF patients under medical care, with such improvement indicating the possibility that the cognitive dysfunction observed in this population might be modifiable. Exploratory analyses were conducted to identify possible mechanisms for cognitive changes.

Abbreviations:

BNP	*Brain natriuretic peptide*
CCS	*Canadian Cardiovascular Society*
CHF	*Chronic heart failure*
EECP	*Enhanced external counter pulsation*
EF	*Ejection fraction*
LV	*Left ventricle*
LVEF	*Left ventricular ejection fraction*
NYHA	*New York Heart Association*
O-SBST	*Oktem Sozel Bellek Surecleri Test*
WAIS-R	*Wechsler Adult Intelligence Scale-Revised*

PATIENTS AND METHODS

Study population

Thirty-six CHF patients (mean age: 66±10 years) with a diagnosis of ischemic cardiomyopathy and CHF between January 2008 and August 2010, who were New York Heart Association (NYHA) Class II-IV and Canadian Cardiovascular Society (CCS) Class II-IV, were enrolled in this study. The subjects were selected in a consecutive fashion. All patients were referred for EECP therapy by the same cardiologist who had been specially trained in this treatment. After explanations, some patients who lived far from the hospital and reported feeling fine declined the EECP therapy. Those patients declining treatment served as the control group. All patients signed a consent form.

While 18 patients constituted the EECP treatment arm, 18 patients who declined EECP treatment served as a control group though they remained on the medical therapy. One patient in the treatment group could not finish his 35-hour EECP program. One patient underwent dialysis due to progression of his chronic renal disease. One patient withdrew his informed consent to participate in the study. One patient declined the second evaluation for cognitive function when the EECP treatment was completed. The remaining 14 patients (14 males, mean age: 64±9 years, range: 53-78 years) served as the treatment group. Eighteen patients (15 males, 3 females, mean age: 64±9 years) served as the control group. The diagnosis of dilated cardiomyopathy was made on the basis of transthoracic echocardiographic findings (Left ventricle [LV] end-diastolic diameter, >56 mm; ejection fraction [EF], <0.45). All patients had documented coronary artery disease. Patients were on anti-anginal and CHF medications.

Exclusion criteria were as follows: patients who had abdominal aortic aneurysm requiring surgical repair, stent-repaired abdominal aortic aneurysm, severe peripheral artery disease, active deep venous thrombosis, significant coagulopathy, severe aortic insufficiency, severe hypertension (≥180/100 mmHg), severe pulmonary hypertension, and decompensated CHF.

The study was conducted in accordance with the Declaration of Helsinki and was approved by our local institutional ethics committee. All patients gave informed consent before entering the study.

EECP treatment protocol

Patients assigned to EECP received 35 1-hour sessions over seven weeks. Three pneumatic cuffs were placed around the lower limbs and buttocks and were inflated sequentially upward at the onset of diastole, and released rapidly and simultaneously before the onset of systole. The protocol-specified applied pressure was at least 280 mmHg and was reached within 5 minutes of the initiation of treatment. Pulse oximeter was monitored continuously during the treatment session, and the subject's clinical status was re-evaluated if the oxygen saturation dropped by ≥4%.

Cognitive measurements

Patients and controls underwent neuropsychological tests, evaluating a wide range of cognitive domains including attention, short- and long-term memory, verbal memory, and executive and visuospatial functions. All tests were applied to both groups by the same blinded neuropsychologist before and after EECP sessions, and the tests were repeated after the 7th-8th week of entering the study. The application took approximately one and a half hours to complete. Attention and working memory were assessed with Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span Test and Wechsler Memory Scale-Revised (WMS-R) Mental Control Subtest. To evaluate short- and long- term memory, WMS Visual Memory Subtest, WMS Episodic Memory Subtest, and Oktem Sozel Bellek Surecleri Test (O-SBST) were applied. O-SBST was developed by Oktem (1992), and research on its reliability and validity has been completed in Turkish samples.[21] O-SBST is used and validated in Turkey; however, it has not been reported as a new test in the literature. O-SBST consists of 15 different words, which are the same as the A list in the Rey Auditory Verbal Learning (AVL) test. The applications including 15 words were read 10 times and required re-call after each reading. First re-call was named immediate memory. However, in the Rey test, these words are used to examine the subject's word learning and short-term memory. In the O-SBST, patients are asked to recite the words to examine their short- and long-term memory. O-SBST is done in three steps to evaluate 1. immediate recall, 2. short-term memory, and 3. long-term memory. At the beginning of the first step, if the patient is unable to recall more than three words, the test is stopped.

The total score of the 10 recall tests was named as short-term memory. After about 40 minutes, patients were asked to repeat the 15 words to evaluate how many of them they remembered. This is referred to as delayed re-call test. If the person is unable to remember these words, a forced-choice checklist is used in which phonemic and semantic clues are included, in order to assist the patient in selecting the correct words (Oktem, 1992). To measure the language domain, the Boston Naming Test was administered.

Verbal fluency was measured by asking the participant to list as many words as possible beginning with the letters K, A, and S and animal names in one minute. Executive functions were assessed with Verbal Fluency Test, Stroop Test, Clock-Drawing Test, and WAIS-R Similarities Subtest. To measure working memory, WAIS and Digit Span Subtests were administered. In the Forward Digit Span Test, patients are asked to recall a series of digits in the same order, while on the backward digit span test, they are asked to recall a series of digits in reverse order. Visuospatial skills were evaluated with Benton Face Recognition Test and Figure Coping Test (Table 1).

Echocardiographic assessment

All participants underwent transthoracic echocardiography by means of an echocardiograph equipped with a broadband transducer (Vivid 7®, GE VingMed UltrasoundAS; Horten, Norway). Measurements of the left atrium, LV, and right ventricle (RV) were obtained from the parasternal long-axis and apical four-chamber views, in accordance with standard criteria. Left ventricular ejection fraction (LVEF) was calculated

Table 1. Cognitive functions and neuropsychological tests

Orientation	Subtest of Mini- Mental State Examination	Total score 5
Memory	Oktem Sozel Bellek Surecleri Test	It has 15 words and was applied 10 times. It evaluates immediate memory, short- and long- term memory and recognition
	WMS-R Visual Memory Subtest	Evaluates short- and long-term memory
	WMS-R Episodic Memory Subtest	
Working memory	WMS-R Mental Control Subtest	The patient recites days and months in reverse and counts back from 20. In addition, the patient counts backward by seven from 100 and counts forward by four to 40.
	Boston Naming Test	It has two scores: Total score: 31 Spontaneous and to follow-up clues
Attention	WAIS-R Digit Span Test	It has two scores: 1. Forward row score (Total score: 8) 2. Backward row score (Total score: 7)
Executive functions	Stroop Test	It has three scores: 1. Perseverative errors 2. Spontaneous correction 3. Interference time (It is informed about disin hibition problem)
	Verbal Fluency Test (Animal, K-A-S)	The patient is given one minute to recite as many words as he can beginning with these letters.
	Clock Drawing Test	Total score: 7
	WMS-R Similarities Subtest	Total score: 20
Visuospatial functions	Benton Face Recognition Test	The patient is required to draw pictures similar to those shown to the patient. Total score: 49
	Figure Copy Test Clock Drawing Test	The patient copies 5 figures. Total score: 15 Total score: 7

WAIS-R: Wechsler Adult Intelligence Scale–Revised; WMS-R: Wechsler Memory Scale-Revised.

using the modified Simpson rule in the apical two- and four-chamber views. Mitral flow was measured from the apical four-chamber view with pulsed-wave Doppler, by placing the sample volume at the tips of the mitral leaflets.

Blood samples

Each patient had fasting blood samples drawn from a large antecubital vein for the determination of brain natriuretic peptide (BNP) values before entering the study and after the 7-8-week study period. The BNP levels were analyzed by means of the Triage® BNP test (Biosite Incorporated; San Diego, CA, USA) within 24 hours after hospitalization. The normal value for the Triage® BNP test was <100 pg/ml.

Statistical Methods

The Statistical Package for the Social Sciences (SPSS) 13.0 was used for statistical analyses of the study. Results are presented as mean±SD or as percentages and numbers for categorical data. In comparing the results between the EECP and control groups of the study, continuous variables that were normally distributed were analyzed with two-tailed t test and unequally distributed variables were analyzed with Mann-Whitney U-test. Categorical data and proportions were analyzed using chi-square. A *p* value <0.05 was considered significant.

RESULTS

The characteristics of the study participants are listed in Table 2. Both groups had similar baseline characteristics. Fourteen patients in the EECP arm and 18 patients in the control group completed the study. After the treatment period, improvement in NYHA functional classification (2.4±0.6 *vs.* 1.5±0.5, p<0.001) and CCS functional classification of angina (1.9±0.6 *vs.* 1.1±0.5, p<0.001) was observed in patients with EECP treatment. LVEF increased from 32±12% to 36±14% (p=0.028), and BNP levels decreased from 826±892 pg/ml to 589±861 pg/ml in patients with EECP treatment (p=0.048) (Table 3).

Results of memory tests

There was no significant difference in the WMS Visual Memory Test score in either group before and after treatment. While short-term memory scores of the WMS-R Story-Memory Test were decreased (basal score: 13.9±5.1, post-treatment score: 10.2±4.0; p=0.028), long-term memory scores of the WMS-R Story-Memory Test did not change in the EECP group before and after the EECP procedure (basal score: 11.8±5.8, post-treatment score: 10.2±4.0; p=NS). Although in the medical treatment group, the changes in short-term memory scores of the WMS-R Story-Memory Test were not statistically significant (basal score: 12.2±2.4, post-treatment score: 11.1±3.7; p=NS), long-term memory scores were significantly lower after treatment (basal score: 11.1±2.9, post-

Table 2. Clinical, echocardiographic and biochemical characteristics before and after the treatment period in the two patient groups

	EECP treatment group (n=14)			Medical treatment group (n=18)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			65±9			66±7	NS
Gender (male/female)	14/0			15/3			NS
NYHA functional class			2.4±0.6			2.0±0.7	NS
CCS angina class			1.9±0.6			1.7±0.8	NS
Blood pressure (mm/Hg)	118/72			123/74			NS
Body mass index (kg/m²)			27±2			29±4	NS
Coronary artery disease	14	100		18	100		NS
Hypertension	7	50		12	67		NS
Diabetes	8	57		13	72		NS
Hyperlipidemia	7	50		11	61		NS
History of smoking	8	57		10	56		NS
Clopidogrel	7	50		4	22		NS
Aspirin	12	86		15	83		NS
Beta-blocker	11	79		15	83		NS
Nitrate	6	43		7	39		NS
Calcium channel blocker	5	36		5	28		NS
ACE-I/ARB	9/4	93		8/6	78		NS
Furosemide	12	86		11	61		NS
LVEF			32±12			28±10	NS
BNP (pg/dl)			826±892			808±960	NS

EECP: Enhanced external counter pulsation; NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society; ACE-I/ARB: ACE-inhibitors/angiotensin-II receptor blockers; LVEF: Left ventricular ejection fraction; NS: Non-significant; BNP: Brain natriuretic peptide.

Table 3. Patients with EECP had improvement in their clinical situation but patients without EECP treatment had no improvement in their clinical situation after treatment

	EECP treatment group (n=14)	*p*	Medical treatment group (n=18)	*p*
NYHA Functional Class		**<0.001**		NS
(before treatment period)	2.4±0.6		2.0±0.7	
(after treatment period)	1.5±0.5		1.8±0.4	
CCS Angina Class		**<0.001**		NS
(before treatment period)	1.9±0.6		1.7±0.8	
(after treatment period)	1.1±0.5		1.4±0.5	
LVEF (%)		0.028		NS
(before treatment period)	32±12		28±10	
(after treatment period)	36±14		28±10	
BNP (pg/dl)		0.048		NS
(before treatment period)	826±892		808±960	
(after treatment period)	589±861		641±689	

EECP: Enhanced external counter pulsation; NYHA: New York Heart Association; NS: Non-significant; CCS: Canadian Cardiovascular Society; LVEF: Left ventricular ejection fraction; BNP: Brain natriuretic peptide.

treatment score: 8.3±4.4; p=0.020) (Table 4).

Results of attention tests

In the EECP group, there was a significant improvement in the forward row score of the attention subtest of WMS, namely digit span forward, compared to their pretreatment scores (basal score: 4.5±0.1, post-treatment score: 5.1±1.2; p=0.020). Changes in the digit span backward part of the same test were not significant (basal score: 2.6±1.1, post-treatment score: 3.3±0.7; p=0.058). The attention subtests of WMS did not differ after the treatment period in the medical treatment group (Table 4).

Results of executive function tests

Interference time of the Stroop Test, which is one of the most important executive function tests, was significantly improved after treatment in the EECP group (basal score: 67.2±23.9, post-treatment score: 53.8±19.3; p=0.012). Change in the Verbal Fluency Test score was not statistically significant when before and after treatment scores were compared (p=NS). The Stroop test and Verbal Fluency Tests of the control group were not statistically significantly changed when before and after treatment scores were compared (Table 4). Although total Boston Naming Test score was improved after the treatment period in the EECP group (basal score: 28.0±3.3, post-treatment score: 29.5±2.5; p=0.041), it was not different in the control group after the treatment period (basal score: 30.1±2.1, post-treatment score: 30.1±1.6; p=NS).

Results of visuospatial functions

After treatment, Figure Copy Subtest of visuospatial function in the control group was significantly increased (basal score: 8.2±4.9, post-treatment score: 11.6±4.2; p=0.028) (Table 4). In the EECP group, visuospatial function score was not changed after treatment compared to before treatment.

DISCUSSION

Although CHF patients had better NYHA functional class, angina class, increased LVEF, and decreased BNP levels after treatment compared to before treatment, the control group did not show similar improvements in those parameters. CHF patients showed an improvement in memory, attention and executive functions of cognition after EECP therapy. The tests evaluated all domains especially executive functions of cognition. The greatest improvement was seen in the total score of the Boston Naming Test, a subtest of the WMS Digit Span Test called Forward and Backward Row Test and Stroop Test (especially interference time), which quantifies naming, episodic memory, attention, and executive functions. On the other hand, patients in the control group showed significant

Table 4. Cognitive tests and results

	EECP treatment group (n=14)		*p*	Medical treatment group (n=18)		*p*
	Basal	Last		Basal	Last	
Memory						
O-SBST						
Immediate memory	4.1±1.5	4.2±0.1	NS	3.9±1.6	4.3±2.1	NS
Recall (short-term memory)	85.8±17.2	81.8±14.4	NS	76.8±21.1	78.9±25.6	NS
Delayed recall (long-term memory)	8.14±3.40	8.90±2.3	NS	8.30±3.10	7.8±4.20	NS
Recognition	13.0±4.2	14.4±1.1	NS	14.5±0.9	14.8±0.4	NS
Boston naming test (total)	28.0±3.3	29.5±2.5	0.041	30.1±2.1	30.1±1.6	NS
Spontaneous	24.1±5.9	26.4±4.2	0.011	24.3±4.3	26.1±3.6	0.017
To follow-up clues	3.6±3.3	3.0±2.7	NS	5.8±4.2	4.0±2.4	0.025
WMS visual memory test						
Short-term recognition	6.6±4.3	6.4±4.7	NS	4.4±4.4	6.7±4.1	NS
Long-term recognition	5.0±5.1	6.21±4.90	NS	3.1±4.5	5.3±4.3	NS
WMS-R story-memory test						
Short-term memory	13.9±5.1	10.2±4.0	0.028	12.2±2.4	11.1±3.7	NS
Long-term memory	11.8±5.8	10.2±4.0	NS	11.1±2.9	8.3±4.4	0.020
Attention						
WMS digit span test						
Forward row score	4.5±0.1	5.1±1.2	0.020	4.6±1.0	5.2±1.1	NS
Backward row score	2.6±1.1	3.3±0.7	0.058	3.1±1.2	3.3±0.9	NS
Working memory score	117±43	104±45	NS	117±23	103±45	NS
Executive function						
Stroop test						
Perseverative errors	6.0±5.90	5.6±10.8	NS	6.3±9.1	1.9±4.6	NS
Spontaneous correction	3.7±3.1	2.9±2.7	NS	2.9±2.3	2.4±2.3	NS
Interference time	67.2±23.9	53.8±19.3	0.012	61.4±11.0	48.4±27.7	NS
Verbal fluency						
Semantic fluency (animals)	16.9±3.90	18.3±5.2	NS	15.2±.4.3	16.2±3.6	NS
Letter fluency (K,A,S)	22.2±9.5	27.1±10.3	0.07	22.9±10.0	25.2±11.4	NS
Fruit-person name	5.0±1.9	5.1±2.3	NS	5.0±2.2	5.9±1.9	NS
Clock drawing Test	6.1±1.60	6.1±1.9	NS	6.0±1.0	6.6±0.8	NS
WAIS-R similarities subtest	12.6±6.9	14.5±4.6	NS	13.8±3.9	17.0±3.0	NS
Visuospatial function						
Benton face recognition test	41.4±3.7	41.1±4.7	NS	42.9±5.9	43.3±3.9	NS
Figure copy test	8.9±5.6	8.6±5.3	NS	8.2±4.9	11.6±4.2	0.028

EECP: Enhanced external counter pulsation; O-SBST: Oktem Sozel Bellek Surecleri Test; NS: Non-significant; WMS-R: Wechsler Memory Scale-Revised; WAIS-R: Wechsler Adult Intelligence Scale-Revised.

improvement in Figure Copy Tests, meaning that visuospatial function domains improved. The mechanisms related to cognitive improvement in the parieto-occipital region might be similar to those of other regions in which improvement in cognitive functions are observed.

We found that short-term memory scores of the WMS-R Story-Memory Test were decreased, while long-term memory scores of the WMS-R Story-Memory Test did not change in the EECP group when scores before and after the EECP procedure were compared. In contrast, in the medical treatment group, short-term memory scores of the WMS-R Story-Memory Test did not change, while long-term memory scores were lower after the treatment period. The reason for the lower short-term memory scores in the EECP group can be related to the functional organization of the short-term memory. Since executive functions are associated with the frontal region, short-term memory is related with associative areas of the brain.[22]

In several studies, it has been reported that CHF patients have poorer performance compared with healthy participants in memory and executive functions.[4,23] The etiopathogenesis of cognitive impairment in heart failure remains largely unknown. The chief etiological hypotheses are intermittent cerebral hypoperfusion and autonomic dysregulation. Evidence for chronic hypoperfusion due to CHF had been published in the literature.[24] Mainly cerebral hypoperfusion and autonomic dysregulation occur in heart failure patients and lead to changes in grey and white matter areas of the brain, which results in cognitive impairment.

End-stage heart failure can cause global brain ischemia concluding in cognitive deficits, which may not be noticeable by the clinician as a neurological deficit but can similarly disrupt the life of the patient. Since current literature reports that approximately 25-80% of individuals with heart failure have impairment in one or more cognitive domains, cognitive impairment in heart failure patients is important because of poor self management and frequent hospitalizations.[4] The most frequently affected cognitive domain is executive function, which allows individuals to process information and make decisions. Impairments in executive function cause decreases in functional status[6] and lead to poor daily living activities due to decision-making inability.[7] In our study, after EECP treatment, mild improvement in executive functions can be the goal factor that increases functional status and improves daily living activities of the CHF patient.

Results of the randomized controlled Prospective Evaluation of EECP in Congestive Heart failure (PEECH) trial showed significant improvement in NYHA functional classification in CHF patients with EECP.[19] In previous studies, it was shown that EECP treatment improves angina in patients with or without systolic heart failure.[25-28] In one study, EECP therapy improved both global LV systolic and diastolic functions in patients with chronic angina pectoris. A significant increase in LVEF was shown with EECP treatment in the above-mentioned study.[29]

In the present study, EECP treatment improved patients' NYHA class, CCS class and LVEF. BNP levels were reduced significantly in the EECP group in our study. Patients without EECP treatment had no statistically significant improvement in NYHA class, CCS class, LVEF, or BNP level at the end of the treatment. It was shown that impaired cardiac function can adversely affect the brain via decreased perfusion. Adjusted global cognitive performance, as well as performance in visuoconstruction and motor speed, was significantly directly associated with LVEF. Patients with low EF had worse cognitive performance, in particular in global and motor speed cognitive scores. Decreased EF may exacerbate cerebral hypoperfusion.[30] It was shown in this study that patients with EECP treatment had higher LVEF and decreased BNP levels, which are signs of better heart function. Levenson et al.[31] reported that EECP therapy reduces carotid arterial stiffness and resistance in patients with stable coronary artery disease and augments carotid blood flow and concomitantly reduces the regional vascular resistance.

In our study, the EECP treatment group also had better cognition after the treatment period. We assumed that the treatment with EECP improved heart functions, which may increase the brain perfusion in grey and white matter, which results in better cognitive functions. Patients in the control group had neither better LVEFs nor lower BNP levels after seven weeks. These recovery differences between the EECP group and control group seemed to support our theory of why EECP and medical treatment had better effects on the executive function of cognition compared to medical treatment alone in ischemic heart failure.

The effect of treatment with EECP on exercise hemodynamics and myocardial stress perfusion in patients with chronic stable angina has been studied. A majority of patients had improved exercise tolerance after EECP treatment, and a similar percentage of patients had improved radionuclide stress perfusion images. Post-EECP, maximal exercise heart rate and blood pressure, while demonstrating a linear relation with exercise duration, did not increase significantly despite the increased exercise duration. This suggests that the increase in exercise duration after treatment with EECP is due to both improved myocardial perfusion and altered exercise hemodynamics. EECP therapy thus appears to exert a "training" effect, decreasing peripheral vascular resistance and the heart rate response to exercise.[32] Short-term cardiac rehabilitation such as four weeks of exercise reduced BNP, independent of LVEF, and improved physical fitness. A decreased level of BNP was inversely related to maximal performance and VO_2 max.[33] Exercises may improve physical functioning among generally healthy older adults,[34] and some exercises helped to improve cognitive functions in the healthy and non-healthy groups.[34-37] We determined that patients with EECP treatment had decreased BNP levels, which may be a sign of better physical performance and better VO2 max levels for this patient group in daily life. It seems that the training effect of EECP may help the improvement in cognitive functions, similar to exercise training. This hypothesis may be supported by the fact that patients in the control group demonstrated no such training effects as seen in the EECP group.

It was recently shown that EECP increased brachial and femoral artery flow-mediated dilation and the nitric oxide turnover/production markers nitrate and nitrite and 6-keto-prostaglandin, whereas it decreased endothelin-1 and the nitric oxide synthase inhibitor asymmetrical dimethylarginine. EECP decreased the proinflammatory cytokines tumor necrosis factor-α, monocyte chemo-attractant protein-1, soluble vascular cell adhesion molecule-1, high-sensitivity C-reactive protein, and the lipid peroxidation marker 8-isoprostane. The authors concluded that EECP has a beneficial effect on peripheral artery flow-mediated dilation and endothelial-derived vasoactive agents in patients with symptomatic coronary artery disease.[38] A correlation has been found between serum nitric oxide levels and cognitive deterioration in patients with dementia.[39] Improvement in cognitive functions may be a result of some parts of those effects as mentioned above, such as better peripheral artery flow-mediated dilation and increased nitric oxide level in patients with ischemic cardiomyopathy who were treated with EECP. Those effects that were above the nitric oxide level, such as improved radionuclide stress perfusion and increased nitric oxide levels, might explain why patients receiving EECP treatment had improved angina symptoms, while those with medical treatment did not. Most of these factors that were discussed above, such as improvement in exercise capacity, less chest pain in daily life and increase in EF, may play a very important role in the improvement in cognitive function in patients with EECP.

It seems that better improvement in cardiac functions and functional status of patients with EECP compared to the control group may be the main reasons for their better recovery in the domains of cognition. Unfortunately, to the best of our knowledge, the effects of EECP on cognition have not been reported to date. To our knowledge, this is the first study to examine the influence of EECP on cognitive deficits in a carefully characterized and diverse sample of heart failure patients. In the current study, we found significant improvement in cognitive functions especially in the executive functions of ischemic heart failure patients. Improvement in executive functions may cause enhancement in daily living activities and quality of life of CHF patients.

Limitations

The results of this study are limited by the small sample size of the participants, and thus limit our ability to generalize the results. The reasons for the small size were 1. EECP treatment is a very long treatment option and takes time, and 2. Administration of the cognitive tests is very time-consuming. Future studies with larger sample sizes are needed to confirm the effects of EECP on cognition.

In conclusion, cognitive deficits represent a common problem that affects patients with systolic heart failure. A number of tests have been used to measure cognitive function in heart failure.[3,5,6,40-42] Memory deficits are most common, followed by a psychomotor slowing and decreased executive function. In this study, we utilized memory, working memory, language, attention, executive functions, and visuospatial functions tests, and examined all six of the cognitive domains most often impaired in heart failure (i.e., attention, working memory, long-term memory, learning, executive function).[6] In the present study, patients with systolic heart failure showed an improvement in memory, visuospatial, executive, and attention domains as an improvement in LVEF, BNP levels, functional class, and angina class. We conclude that EECP and medical treatment together demonstrated better effects on cognitive functions than medical treatment alone, but also in daily living activities and functional income in patients. It seems that EECP and medical treatment together could be a new treatment option to improve cognitive function in patients with systolic heart failure.

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REFERENCES

1. Park HS, Kim H, Sohn JH, Shin HW, Cho YK, Yoon HJ, et al. Combination of uric acid and NT-ProBNP: a more useful prognostic marker for short-term clinical outcomes in patients with acute heart failure. Korean J Intern Med 2010;25:253-9. [CrossRef]
2. Zuccalà G, Onder G, Pedone C, Cocchi A, Carosella L, Cattel C, et al. Cognitive dysfunction as a major determinant of disability in patients with heart failure: results from a multicentre survey. On behalf of the GIFA (SIGG-ONLUS) Investigators. J Neurol Neurosurg Psychiatry 2001;70:109-12. [CrossRef]
3. Trojano L, Antonelli Incalzi R, Acanfora D, Picone C, Mecocci P, Rengo F; Congestive Heart Failure Italian Study Investigators. Cognitive impairment: a key feature of congestive heart failure in the elderly. J Neurol 2003;250:1456-63. [CrossRef]
4. Bennett SJ, Sauvé MJ. Cognitive deficits in patients with heart failure: a review of the literature. J Cardiovasc Nurs 2003;18:219-42. [CrossRef]
5. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 2007;9:440-9. [CrossRef]
6. Antonelli Incalzi R, Trojano L, Acanfora D, Crisci C, Tarantino F, Abete P, et al. Verbal memory impairment in congestive heart failure. J Clin Exp Neuropsychol 2003;25:14-23.
7. Dickson VV, Deatrick JA, Riegel B. A typology of heart failure self-care management in non-elders. Eur J Cardiovasc Nurs 2008;7:171-81. [CrossRef]
8. Rich MW. Management of heart failure in the elderly. Heart Fail Rev 2002;7:89-97. [CrossRef]
9. Bennett SJ, Sauvé MJ, Shaw RM. A conceptual model of cognitive deficits in chronic heart failure. J Nurs Scholarsh 2005;37:222-8. [CrossRef]
10. Keary TA, Gunstad J, Poppas A, Paul RH, Jefferson AL, Hoth KF, et al. Blood pressure variability and dementia rating scale performance in older adults with cardiovascular disease. Cogn Behav Neurol 2007;20:73-7. [CrossRef]
11. Schmidt R, Fazekas F, Offenbacher H, Dusleag J, Lechner H. Brain magnetic resonance imaging and neuropsychologic evaluation of patients with idiopathic dilated cardiomyopathy. Stroke 1991;22:195-9. [CrossRef]
12. Kozdag G, Ciftci E, Vural A, Selekler M, Sahin T, Ural D, et al. Silent cerebral infarction in patients with dilated cardiomyopathy: echocardiographic correlates. Int J Cardiol 2006;107:376-81. [CrossRef]
13. Almeida JR, Alves TC, Wajngarten M, Rays J, Castro CC, Cordeiro Q, et al. Late-life depression, heart failure and frontal white matter hyperintensity: a structural magnetic resonance imaging study. Braz J Med Biol Res 2005;38:431-6.
14. Alves TC, Rays J, Fráguas R Jr, Wajngarten M, Meneghetti JC, Prando S, Busatto GF. Localized cerebral blood flow reductions in patients with heart failure: a study using 99mTc-HMPAO SPECT. J Neuroimaging 2005;15:150-6. [CrossRef]
15. Lee CW, Lee JH, Kim JJ, Park SW, Hong MK, Kim ST, et al. Cerebral metabolic abnormalities in congestive heart failure detected by proton magnetic resonance spectroscopy. J Am Coll Cardiol 1999;33:1196-202. [CrossRef]
16. Paul RH, Gunstad J, Poppas A, Tate DF, Foreman D, Brickman AM, et al. Neuroimaging and cardiac correlates of cognitive function among patients with cardiac disease. Cerebrovasc Dis 2005;20:129-33. [CrossRef]
17. Manchanda A, Soran O. Enhanced external counterpulsation and future directions: step beyond medical management for patients with angina and heart failure. J Am Coll Cardiol 2007;50:1523-31. [CrossRef]
18. Soran O, Kennard ED, Bart BA, Kelsey SF; IEPR Investigators. Impact of external counterpulsation treatment on emergency department visits and hospitalizations in refractory angina patients with left ventricular dysfunction. Congest Heart Fail 2007;13:36-40. [CrossRef]
19. Feldman AM, Silver MA, Francis GS, Abbottsmith CW, Fleishman BL, Soran O, et al. Enhanced external counterpulsation improves exercise tolerance in patients with chronic heart failure. J Am Coll Cardiol 2006;48:1198-205. [CrossRef]
20. Kitsou V, Xanthos T, Roberts R, Karlis GM, Padadimitriou L. Enhanced external counterpulsation: mechanisms of action and clinical applications. Acta Cardiol 2010;65:239-47. [CrossRef]
21. Oktem-Tanör O, Baykan-Kurt B, Gürvit IH, Akman-Demir G, Serdaroğlu P. Neuropsychological follow-up of 12 patients with neuro-Behçet disease. J Neurol. 1999;246:113-9. [CrossRef]
22. Fakhri M, Sikaroodi H, Maleki F, Ali Oghabian M, Ghanaati H. Age-related frontal hyperactivation observed across different working memory tasks: an fMRI study. Behav Neurol 2012;25:351-61.
23. Pressler SJ. Cognitive functioning and chronic heart failure: a review of the literature (2002-July 2007). J Cardiovasc Nurs 2008;23:239-49. [CrossRef]
24. Vogels RL, Oosterman JM, Laman DM, Gouw AA, Schroeder-Tanka JM, Scheltens P, et al. Transcranial Doppler blood flow assessment in patients with mild heart failure: correlates with neuroimaging and cognitive performance. Congest Heart Fail 2008;14:61-5. [CrossRef]
25. Loh PH, Cleland JG, Louis AA, Kennard ED, Cook JF, Caplin JL, et al. Enhanced external counterpulsation in the treatment

of chronic refractory angina: a long-term follow-up outcome from the International Enhanced External Counterpulsation Patient Registry. Clin Cardiol 2008;31:159-64. [CrossRef]
26. Michaels AD, Linnemeier G, Soran O, Kelsey SF, Kennard ED. Two-year outcomes after enhanced external counterpulsation for stable angina pectoris (from the International EECP Patient Registry [IEPR]). Am J Cardiol. 2004;93:461-4. [CrossRef]
27. Soran O, Kennard ED, Kfoury AG, Kelsey SF; IEPR Investigators. Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from The International EECP Patient Registry). Am J Cardiol 2006;97:17-20. [CrossRef]
28. Arora RR, Shah AG. The role of enhanced external counterpulsation in the treatment of angina and heart failure. Can J Cardiol 2007;23:779-81. [CrossRef]
29. Esmaeilzadeh M, Khaledifar A, Maleki M, Sadeghpour A, Samiei N, Moladoust H, et al. Evaluation of left ventricular systolic and diastolic regional function after enhanced external counter pulsation therapy using strain rate imaging. Eur J Echocardiogr 2009;10:120-6. [CrossRef]
30. Gottesman RF, Grega MA, Bailey MM, Zeger SL, Baumgartner WA, McKhann GM, et al. Association between hypotension, low ejection fraction and cognitive performance in cardiac patients. Behav Neurol 2010;22:63-71.
31. Levenson J, Simon A, Megnien JL, Chironi G, Gariepy J, Pernollet MG, et al. Effects of enhanced external counterpulsation on carotid circulation in patients with coronary artery disease. Cardiology 2007;108:104-10. [CrossRef]
32. Lawson WE, Hui JC, Zheng ZS, Burgen L, Jiang L, Lillis O, et al. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? Cardiology 1996;87:271-5. [CrossRef]
33. Berent R, von Duvillard SP, Crouse SF, Auer J, Green JS, Sinzinger H, et al. Short-term residential cardiac rehabilitation reduces B-type natriuretic peptide. Eur J Cardiovasc Prev Rehabil 2009;16:603-8. [CrossRef]
34. Taylor-Piliae RE, Newell KA, Cherin R, Lee MJ, King AC, Haskell WL. Effects of Tai Chi and Western exercise on physical and cognitive functioning in healthy community-dwelling older adults. J Aging Phys Act 2010;18:261-79.
35. Wang W, Sawada M, Noriyama Y, Arita K, Ota T, Sadamatsu M, et al. Tai Chi exercise versus rehabilitation for the elderly with cerebral vascular disorder: a single-blinded randomized controlled trial. Psychogeriatrics 2010;10:160-6. [CrossRef]
36. Davis CL, Tomporowski PD, McDowell JE, Austin BP, Miller PH, Yanasak NE, et al. Exercise improves executive function and achievement and alters brain activation in overweight children: a randomized, controlled trial. Health Psychol 2011;30:91-8. [CrossRef]
37. Yamada M, Aoyama T, Tanaka B, Nagai K, Ichihashi N. Seated stepping exercise in a dual-task condition improves ambulatory function with a secondary task: a randomized controlled trial. Aging Clin Exp Res 2011;23:386-92.
38. Braith RW, Conti CR, Nichols WW, Choi CY, Khuddus MA, Beck DT, et al. Enhanced external counterpulsation improves peripheral artery flow-mediated dilation in patients with chronic angina: a randomized sham-controlled study. Circulation 2010;122:1612-20. [CrossRef]
39. Corzo L, Zas R, Rodríguez S, Fernández-Novoa L, Cacabelos R. Decreased levels of serum nitric oxide in different forms of dementia. Neurosci Lett 2007;420:263. [CrossRef]
40. Almeida OP, Tamai S. Congestive heart failure and cognitive functioning amongst older adults. Arq Neuropsiquiatr 2001;59:324-9. [CrossRef]
41. Tanne D, Freimark D, Poreh A, Merzeliak O, Bruck B, Schwammenthal Y, et al. Cognitive functions in severe congestive heart failure before and after an exercise training program. Int J Cardiol 2005;103:145-9. [CrossRef]
42. Hoth KF, Poppas A, Moser DJ, Paul RH, Cohen RA. Cardiac dysfunction and cognition in older adults with heart failure. Cogn Behav Neurol 2008;21:65-72. [CrossRef]

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