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Exercise and Cognitive Training as a Strategy to Improve Neurocognitive Outcomes in Heart Failure: a pilot study

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Abstract

Background: Mild cognitive impairment, especially memory loss, is prevalent in patients with heart failure and contributes to poor clinical outcomes and higher mortality.

Methods: This study evaluated a combined aerobic exercise and cognitive training (Ex/CT) program on memory, executive function, attention, processing speed and reaction time compared to exercise only (Ex) or an attentional control usual care (UCAC) stretching and flexibility program. Participants completed a standardized neurocognitive battery at baseline, 3 and 6 months along with demographic, clinical, and functional capacity (six-minute walk test [6MWT]). A linear mixed model analysis was used with comorbidity as a covariate.

Results: Sixty-nine participants were enrolled, the mean age was 61±10, 54% were female, 55% were African American and the mean LVEF% was 35±15. A significant group by time interaction for verbal memory was found at 3 months (F [2, 53] = 4.3, p=0.018) but was not sustained at 6-months in the Ex/CT group. Processing speed/attention differed across treatment groups between BL and 6 months, but improvement occurred among UCAC participants. There was also significant group differences in the 6MWT distance occurring at 3 months (F [2, 52] = 3.5, p=0.036), however significant improvement was observed within the Ex/CT group only. There were no significant differences in 6MWT in the other groups at 3 or 6 months.

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Conclusions: An Ex/CT intervention was associated with improved memory in persons with HF and warrants further investigation in a larger trial. The relationship between functional capacity and cognitive function also needs further study.

Keywords

heart failure; exercise; cognitive training; mild cognitive impairment

Introduction

Mild to moderate cognitive impairment (MCI) is estimated to occur in 25% to 50% of stable chronic heart failure (HF) patients and is associated with adverse clinical outcomes, poor quality of life and higher mortality.[1] Heart failure negatively impacts function in most cognitive domains.[2–3] Memory loss, the most common cognitive deficit in HF, is particularly challenging because of its negative impact on the individual's capacity to participate in essential self-care activities such as managing complex medication regimens and adhering to dietary restrictions.[4] The cognitive decline experienced in HF is greater than normal aging, but lacks other symptoms of dementia, such as impaired judgment, reasoning or difficulties performing activities of daily living. An MCI diagnosis requires abnormalities to be present on neuropsychological testing (1.5 SD below age-standardized mean) in at least one cognitive domain.[5] In an observational study, persons with HF had lower performance on neurocognitive tests than those without HF, and if MCI was present, they were twice as likely to progress to dementia.[6]

Low cerebral blood flow and oxygenation are thought to be the primary physiological mechanisms that contribute to cognitive decline in HF.[7–8] Imaging studies also support structural brain and tissue changes including white matter-hyper-intensities, reductions in neuronal volume in frontal, temporal and parietal lobes, decreased axonal integrity and alterations in myelin structure.[9–10] Despite the increasing awareness of the high prevalence and adverse outcomes associated with MCI and memory loss in HF, there are currently no evidenced-based guidelines available to address this growing problem. Several small studies have shown that aerobic exercise and cognitive training improves neurocognitive outcomes in persons with HF, but none have tested the combined efficacy of both strategies.[11–13] To address this gap, the Exercise and Cognitive Training Intervention in HF (EXCITE-HF), a randomized controlled trial, was conducted in persons with stable New York Heart Association (NYHA) class II and III HF. The primary aim of the study was to evaluate the efficacy of an aerobic exercise and cognitive training intervention on memory compared to exercise alone or an attention control usual care group receiving a stretching and flexibility program. We hypothesized participants in the combined program would have the greatest improvement in memory.

Methods

Design and Procedures

A three-group pre-post randomized controlled design was used to evaluate intervention efficacy with data collected at baseline, 3-and 6-months. The protocol was approved by the

university institutional review board and all participants provided written informed consent before participation. Data were collected from December 2014 to October 2016. Once baseline measurements were completed, participants were randomized using a table of random numbers prepared by a statistician. Participants were assigned to receive a usual care attention control stretch and flexibility program (UCAC, n=19), an exercise only intervention (EX, n=29), or exercise + cognitive training (EX/CT, n=21) for 3 months. Data collection was conducted by trained research assistants (RAs) blinded to group assignment. The study neuropsychologist selected the neurocognitive battery and trained the research staff in the administration and scoring of the standardized tests.

Sample

Participants were screened for eligibility using an electronic medical record. To be eligible, participants had to be ambulatory, between 40–75 years of age, have a left ventricular ejection fraction (LVEF) ≥ 10% documented within the last year by echocardiogram, cardiac catheterization ventriculography, or radionuclide ventriculography, stable NYHA class II-III HF, receiving medication therapy for HF according to the American College of Cardiology/ American Heart Association recommendation guidelines[14] for at least 3-months prior to study enrollment. Participants also had to be English speaking and live independently. In addition, participants had to score ≤ 26 on the Montreal Cognitive Assessment (MOCA)[15] and have access to a computerized device. Exclusions included those with unstable angina or hypertension, end-stage organ failure, and any identified or diagnosed neurological or psychological disorder that would interfere with physical or cognitive functioning.

Because of the limited sample size and lack of effect size estimates, a traditional power calculation was not performed. Rather, we analyzed data with the specific intent of establishing population parameters (e.g., effects sizes) for the variables being investigated. However, preliminary power calculation indicated that the relatively small sample size of n=69 at 80% power, and α=.05, we were powered to detect a moderate (d=.5) to large effect size (d=.8).

Interventions

Exercise Only Program.—A home-based aerobic exercise program was used; participants were instructed to walk 3 times per week for 24 weeks. Dose-specific exercise was based on maximum heart rate (HR) obtained during the baseline modified Balke treadmill test.[16] Each participant was provided a target heart rate (THR) of 60% to 70% of maximum HR achieved on the cardiopulmonary exercise test (CPET) for the exercise prescription. Two home-visits by the research team after baseline testing was conducted to provide instructions on the Polar HR monitor[17] and Omron pedometer[18] for tracking THR and steps, respectively. In addition, the participant received instructions on how to complete a written walking log to document adherence to the intervention. Under weekly telephone supervision by a member of the research team, participants began the walking sessions at 60% of THR for 30 minutes, increasing to 70% intensity and 45-minutes duration over the next 4-weeks. Participants were followed by telephone for the first 12-weeks, then bi-monthly for the remainder of the follow-up period.

Combined Exercise and Cognitive Training (EX/CT) Program

The same aerobic exercise walking instruction was provided to the combined Ex/CT group as discussed above. The Brain Fitness (Posit, San Francisco, CA detailed below) computerized program was used for the cognitive training component.[19] The program is based on the principles of neuroplasticity and is designed to enhance sensory integration and strengthens capability for encoding information. Research to date has found: 1) participants with limited or no computer experience were capable of learning to perform the training exercises, 2) the training was safe and well tolerated by participants, and 3) healthy participants who trained on Brain Fitness showed on average a 1/3 standard deviation improvement in memory, concentration and cognition, and 4) it has been tolerated well in patients with HF in 2 prior studies.[12–13,19] The Brain Fitness program is designed to be completed over 8-weeks in 40-one-hour sessions.[19] During 2 home visits, research staff provided training and demonstrated how to use the Brain Fitness program with a return demonstration provided by the participant. In the current study, all participants were provided free access to the Brain Fitness program and completed the computerized program at home.

Usual Care Attention Control: Stretching and flexibility exercise

Education, flexibility and stretching protocols were provided to controls as a time-equivalent, placebo exercise condition. Participants received a home visit to review the standardized HF educational materials. The flexibility and stretching movements were also demonstrated by the research staff during the home visits with a return demonstration by the participant. In pilot evaluations, the stretching and flexibility movements had high satisfaction and were well received but were not strong enough to influence study outcomes.[20] The attention control stretching and flexibility program was delivered within 2-weeks after baseline measures were completed and participants were instructed to complete the program 2–3 times per week over the next 24-weeks. Weekly telephone calls were made for 12-weeks to discuss educational materials and to answer questions about the stretching and flexibility movements followed by bi-monthly up to 24-weeks post-baseline.

Adherence

To be 100% adherent for the exercise sessions, participants in the EX groups were required to document walking 3 times per week at the prescribed intensity/duration on the exercise log. Participants recorded exercise sessions on a calendar and included maximum HR achieved, rate of perceived exertion (RPE)[21] during walking and number of steps during the walking sessions. Polar HR monitors and pedometers were also used to objectively document exercise intensity (i.e., maximum HR and RPE achieved), duration, walking adherence and progression. After this time-period, participants completed walking logs and received telephone calls weekly to discuss their walking progression and to change the prescription as indicated and described above.

Adherence for the Brain Fitness intervention was evaluated by the number and duration of sessions automatically logged when the participant accessed the program. Time to complete the entire program was pre-established by Posit Science to be 2310 minutes.[19] Participants were considered adherent if they completed 80% or 1848 minutes of the program of the 12-

week intervention period which was approximately three times per week for 180 minutes total.

Measures

Socio-demographic and clinical characteristics were validated using the electronic medical record (Table 1). The Charlson Comorbidity Index[22] was used to assess the number and severity of comorbid diseases. Participants with a LVEF < 40% were categorized as heart failure with reduced ejection fraction (HFrEF), those with LVEF at 40–50% were categorized as HF with midrange ejection fraction (HFmrEF) and those with a LVEF above 50% were characterized as HF with preserved ejection fraction (HFpEF).[14,23] HF etiology and type were validated in the participant's medical record.

Aerobic and functional capacity—The modified Balke maximal symptom-limited treadmill test[16] and the six-minute walk test (6MWT)[24] were used to determine aerobic and functional capacity, respectively. Peak oxygen consumption (VO_{2peak}) was obtained using continuous gas exchange according to the American Heart Association guidelines.[25] The 6MWT was administered using a standardized protocol where participants walked back and forth on a 100-foot flat, level hall-way.[26–27]

Cognitive screening assessment—Prior to enrollment, participants were screened for global cognitive function and to determine study eligibility using the Montreal Cognitive Assessment (MoCA).[15] The MoCA was selected as the screening tool since it assesses visuospatial and executive deficits that are more reflective of vascular cognitive impairment in HF, compared to other global cognitive measures such as the Mini-Mental Status Examination (MMSE).[28] Validity of the MoCA has been previously reported in HF patients.[13] Scores range between 0 and 30, with a score of 26 to 30 considered normal or no MCI present. In the current study, participants had to have MoCA scores of ≤ 26 to be eligible for participation. The lower the score the greater the cognitive impairment.

Neurocognitive Outcome Variables—Standardized neurocognitive tests were administered by trained research staff and used to evaluate memory, processing speed, attention and reaction time. Extensive training on how to administer the neurocognitive battery occurred before study enrollment by 2 clinical psychologists with expertise in this area. Fidelity checks were also conducted to ensure the neurocognitive tests were administered consistently. The neurocognitive tests were administered in the patients' home at baseline, 3-and 6-months using a standardized script. When available, alternate versions of each test were used at the different time points to aid in reducing the effects of practice from repeated test administration. Raw scores for selected neurocognitive tests were first converted to z-scores at each time point and then combined into cognitive domains. The neurocognitive tests are briefly described in Table 1.

Depressive Symptoms—The Beck Depression Inventory II (BDI-II),[35] a 21-item instrument with scores ranging from 0 to 63, was used to measure depressive symptoms. Higher scores reflect greater depressive symptoms over the past 2 weeks. This instrument

has been used extensively in patients with cardiovascular disease and in HF to measure depressive symptoms.[36]

Statistical Analysis—Baseline descriptive statistics were computed for the socio-demographic, clinical and study variables and compared across study groups. Analysis of variance (ANOVA) and chi-square tests were used to examine differences between the three study groups on all demographic, clinical and outcome variables. Linear mixed effects models were used for testing preliminary efficacy of the intervention on the outcomes of interest over time. Separate models were fitted for individual outcomes to assess group, time and group by time interaction effects, where a significant group by time interaction is indicative of a differential effect of the intervention across groups. Analyses were first unadjusted for any baseline characteristics and then adjusted for comorbidity due to baseline differences between groups. Pairwise differences between time points were used to evaluate within-group changes from baseline to 3-months, 3 to 6 months and baseline to 6-months and Bonferroni correction was used for multiple comparisons. Effect size measures (Cohen's d) were calculated using the standard method of dividing the mean difference scores by the placebo group baseline standard deviation.[37] Missing data patterns were assessed at each time point. An intent to treat approach was used for data analysis. All subjects with partial and complete data contributed to the likelihood calculation of the mixed effects models. Adherence to the exercise and cognitive training interventions were analyzed using descriptive statistics. Analyses were performed using version 24 of SPSS software.

RESULTS

A total of 952 individuals were screened for study participation, 807 were deemed ineligible, 76 declined and 69 were enrolled (Figure 1). Baseline sociodemographic and clinical characteristics are presented in Table 2. There were a greater number of comorbidities in the EX group and was controlled as a covariate. The mean age of the sample was 61 ± 10 years, the majority were female (n=37, 54%), African American (n=38, 55%) and most were highly educated. Clinically, the majority were categorized as NYHA class II (n= 38, 55%), 53% (n=36) had an implanted device such as a defibrillator or pacemaker. The mean LVEF was 35 ± 15% with a range of 10%–65%, indicating the presence of reduced HFrEF (n= 42, 61%), preserved (HFpEF) (n=19, 28%) and mid-range HFmrEF (n=8, 12%).

The neurocognitive scores of participants adjusted for baseline comorbidities are presented in Table 3. Over the first three months, verbal memory had a significant group by time interaction, with improvement in the intervention groups (both Ex and Ex/CT) compared to the control group (Table 3). However, the effect was no longer significant over the following three months. Within the UCAC group, verbal memory significantly declined from BL to 3-months (*mean difference* = −0.40, *SE* = 0.17, $t(51) = -2.35$, $p = .025$), however the effect was no longer significant at 6 months. The results were adjusted for multiple comparisons using Bonferroni correction when comparing between multiple groups or over time. There was also a significant interaction effect (group × time interaction) for processing speed/attention over a longer period, between BL and 6 months, but not between BL and 3 months (Table 3). Effect size estimates (Cohen's d measures), indicated by standardized mean differences of groups at 3 months and 6 months are given in Table 4. Moderate to large differences in

means for verbal memory (at 3 months) for the EX only and Ex/CT groups compared to UCAC and processing speed/attention (at 6 months). Reaction time had a moderate effect size comparing Ex/CT with the UCAC group as well, all other neurocognitive effect sizes were small.

Overall, there were significant group differences over time indicated by significant group × time interaction for 6MWT distance (Table 3). Specifically, the Ex/CT intervention had a positive effect on 6MWT distance at 3 months compared to the UCAC group (*mean difference* = 75.97 meters, *SE* = 29.12, $t(95) = 2.61$, $p = .032$). Within the Ex/CT group, the improvement in total 6MWT distance was greater at 3 months (*mean difference* = 52.24 meters, *SE* = 18.85, $t(54) = 2.77$, $p = .008$), but not sustained at 6-months. There were no significant differences in walk distance in the EX only or attention control groups at 3 or 6 months. The effect size was also moderate for the 6MWT comparing Ex/CT to UCAC Cohen's *d* (0.75) compared to small changes (0.19) in the EX only group (Table 4).

Mean scores on the BDI-II showed participants were experiencing mild depressive symptoms. However, based on a wide range of scores from 0–44, it was evident that some participants were experiencing moderate to severe depressive symptoms at baseline. While there were no differential group effects over time at both 3 and 6 months (Table 3), there was a significant time effect indicating overall reduction in the depressive symptoms by 3 (*mean difference* = −2.00, SE = 0.85, $t(78) = -2.35$, $p = .042$) and 6 months (*mean difference* = −3.04, *SE* = 0.89, $t(77) = -3.37$, $p = .002$).

Adherence rates to the walking program, or participants exercising 3 or more days per week, was 60% with 27% being moderately adherent walking a minimum of 2 times per week. Approximately 10% were non-adherent and did not engage in the walking program. Seventeen out of 22 participants were engaged in the Brain Fitness exercises. Participants who played the computerized games for an average of 3 days and over 180 minutes total per week were 80% adherent.

DISCUSSION

This study demonstrated that a 3-month home-based combined program of exercise and cognitive training was associated with significant improvement in verbal memory compared to an exercise only and a usual care stretching and flexibility attention control group. To our knowledge, no previous study has reported the effects of a combined aerobic exercise and cognitive training intervention on neurocognitive outcomes in persons with HF. Two small studies conducted by Pressler et al.[12–13] examined the effects of a cognitive training intervention using the same plasticity-based cognitive training program, Brain Fitness. In the first study, improvement in delayed recall memory (p = .032) was reported among the 17 participants completing the 12-week intervention.[12] Among 13 persons in the second study who received the Brain Fitness program, there was significant improvement in working memory over the 8-week intervention with no additional changes observed at the 12-week measurement time point.[13] Improved verbal memory in the present study is consistent with these findings and suggests computerized plasticity or other cognitive training programs training may be an effective strategy for improving memory in persons with HF. Future

studies comparing both intervention components in an adequately powered clinical trial is warranted.

Only one small study examined the effects of aerobic exercise on neurocognitive function in HF. Tanne et al.,[11] compared the effects of an aerobic exercise program on neurocognitive function in 20 persons with NYHA class III HF to 5 controls unable to participate in the program. Compared to controls, those completing a traditional 18-week cardiac rehabilitation program had shorter completion times on Trail-making A and B and Stroop Part A tests, which reflected significant improvements in processing speed and attention. The standardized cardiac rehabilitation program used in the Tanne et al.[11] study was longer in duration which may have conferred a higher dose of exercise. In another study by Stanek et al.,[38] improvements in verbal memory were associated with higher metabolic equivalents (METs), a measure of the activity intensity, among participants with cardiovascular disease including individuals with HF attending a 12-week cardiac rehabilitation program. Most studies evaluating neurocognitive function in healthy adults and HF have focused on aerobic exercise with few examining other modalities of exercise such as resistance training. Combined aerobic and resistance exercise and resistance exercise alone have also shown efficacy for improving cognition.[39] Evidence increasingly suggests that MCI associated with HF may be modifiable and that higher functional capacity contributes to better neurocognitive functioning likely through increased cerebral blood flow.[1,9] The benefits of aerobic exercise are well-established to partially reverse the debilitating peripheral musculoskeletal alterations in HF and may also contribute to improved cognitive function through some of these same underlying mechanisms.

The mean 6MWT distance of 340 meters at baseline was lower than previously reported[40] and 43% (n=30) walked 300 meters or less. A 6MWT distance of less than 300 meters has been associated with greater disease severity, higher hospital readmission rates and mortality in HF.[41] The role that the 6-minute walk distance plays in relation to cognitive function in persons with HF is unknown. In the current study, a clinically meaningful change of greater than 50 meters in 6MWT distance in the EX/CT group may have translated to better memory.[42] In a large trial (N=2043) examining Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF), the six-minute walk distance, but not LVEF or NYHA class, was an important predictor of global cognitive function (MMSE) in persons with HFrEF.[43] Among 80 elderly adults with ischemic HFrEF, Baldasseroni et al., 2010[44] also found a positive association between 6-minute walk distance with the MMSE. Routine evaluation of functional capacity using simple performance tests such as the 6MWT may help identify those at high risk for future cognitive and physical function decline.

Strengths and Limitations

This study had several strengths including participants being willing to undergo comprehensive, standardized neurocognitive testing at 3-time points which has not been well documented in persons with HF. Notably, none of the participants had been screened for cognitive impairment prior to enrolling in the study but joined the study because they perceived their memory had declined. The findings from the current study extend this

research to a broader population that includes African American females with lower global cognition and functional capacity.

Study limitations included a relatively small sample size and not adequately powered to determine group differences. Larger trials are needed to determine whether these intervention strategies are clinically beneficial. We were unable to directly download exercise data which may have contributed to measurement error. Attrition rates were moderate to high, especially in the 2 intervention groups. The reasons are unclear but may have reflected a sicker HF population since they were being seen at a large, academic referral center.

Although previous studies have cited high satisfaction and adherence to the Brain Fitness program,[15–16] satisfaction among the current study participants was low. Participation and adherence declined among many in the study as the computerized games became more challenging. The ability to adhere to the CT may have reflected better baseline cognitive functioning. Among individuals with low global function and low literacy, cognitive reserve may have been too limited to successfully engage in the Brain Fitness program. Some of our participants had limited use of computers which also may have influenced their ability to engage in this type of intervention. Although we used a placebo exercise condition that included stretching and flexibility movements, a sham computer program would have better equalized the intervention groups in relation to the CT intervention.

In conclusion, participants completing the combined exercise and computerized training program improved verbal memory at 3 months. In the current study, many participants had MOCA scores that reflected moderate cognitive impairment. Cut-off scores for baseline cognitive screening tests are warranted in future trials to ensure that participants less likely to be responsive to change are not enrolled. As the population ages, interventions that address cognitive and functional impairments will be paramount for observing gains in daily life and optimizing quality of life.

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No Disclosures to Report

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Highlights

- The primary aim of this study was to evaluate the efficacy of an aerobic exercise (walking) and cognitive training intervention on cognitive function compared to exercise alone or an attention control usual care group receiving a stretching and flexibility program in stable New York Heart Association class II and III heart failure participants with mild cognitive impairment.
- The main finding of the study was that participants in the combined aerobic exercise and cognitive training program had significant improvement in verbal memory at 3 months and a trend for sustained improvement at 6-months compared to exercise alone or the attention control usual care groups. In addition, the combined group also had significant improvement in the six minute walk distance at 3 months compared to the other groups.
- There is very limited evidence that exercise or cognitive training is associated with improvement of mild cognitive impairment in heart failure. This study provides evidence that a combined approach may be superior to either strategy alone for improving cognitive function in persons with stable heart failure. Large, high-quality randomized trials are needed to determine if the beneficial effects of these intervention strategies are associated with improvement in mild cognitive impairment or slows the progression to dementia.

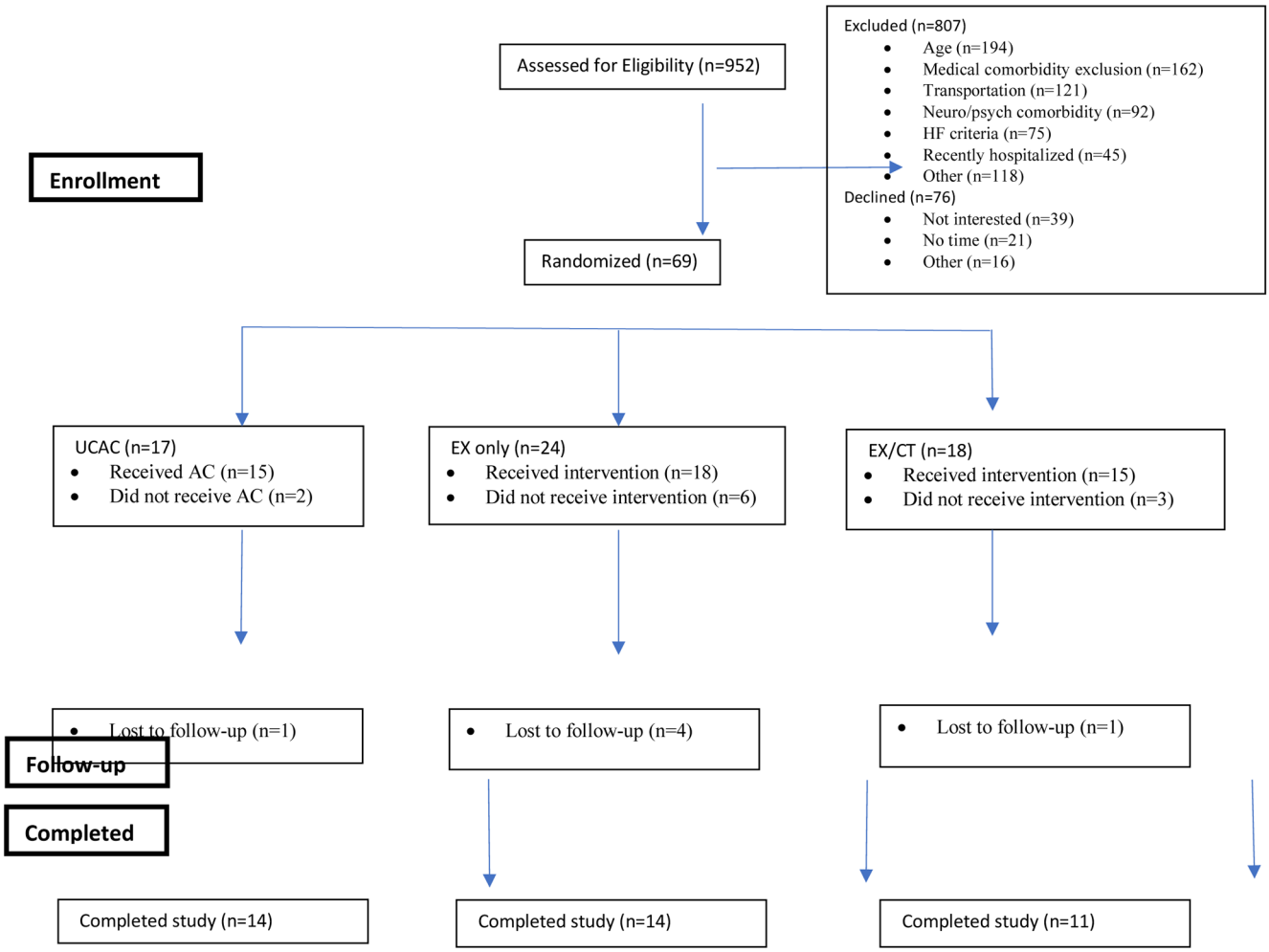

Figure 1.
Consort flowchart.

Table 1.

Neurocognitive domains and Measures

Neurocognitive Domain	Measures
Global cognition	Montreal cognitive Assessment (MoCA)[18] evaluates attention, memory, language and executive function.
Verbal Memory	List Learning, List Recall, and List Recognition subtests from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS); these subtests measure immediate memory, learning, delayed memory and recognition memory.[31]
Visual Memory	RBANS figure recall requires the participant to remember a recent figure and redraw it from memory.[31]
Processing Speed/Attention	RBANS coding measures attention. This test requires the rapid copying of numbers derived from a key of symbols. The Color Trails Test[36] (CTT) Part I, participants rapidly connect numbered circles in sequence (1 through 25). The length of time to complete each part is recorded, along with any errors, near-misses, and prompts required during the test.
Working Memory	Digit Span and Letter Number Sequencing subtests from the Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV).[35] The Digit Span subtest require the repetition of verbally presented series of numbers that increase in length; trials include the repeating of numbers in forward, backward, and numerical order. The Letter-Number sequencing test requires the repeating strings of letters and numbers in numerical and then in alphabetical order. Color Trails Test[36] (CTT) Part 2, participants rapidly connect numbered circles in sequence while alternating between pink and yellow circles.
Reaction time	The California Computerized Assessment Package[37] (CalCap) is a software program that measures several cognitive domains, including reaction time, divided attention, recognition memory, and rapid visual scanning. Scores are standardized based on age and education level norms.

Table 2.

Baseline Sociodemographic and Clinical Characteristics of UCAC, EX and EX/CT groups.

Characteristics	UCAC (n=19)	EX only (n=29)	EX/CT (n=21)	Df/ (df1, df2)[a]	P-value[b]
Age, mean ± SD	59 ± 11	60 ± 10	63 ± 9	2, 66	0.39
Sex, (n,%)				2	
Men	7 (37)	12 (41)	13 (62)		0.22
Women	12 (63)	17 (59)	8 (38)		
Race, n (%)				4	
African American	13 (68)	16 (55)	9 (43)		
Caucasian	4 (21)	12 (41)	11 (52)		0.31
Other	2 (11)	1 (3)	1 (5)		
Education, y, mean ± SD	14 ± 2	14 ± 3	14 ± 3	2, 54	0.89
NYHA class, n (%)				2	
II	13 (68)	14 (48)	11 (52)		0.37
III	6 (32)	15 (42)	10 (48)		
LVEF, %, mean ± SD	36 (14)	34 (14)	34 (19)	2, 66	0.93
ICD, n (%)	7 (37)	7 (24)	11 (52)	2	0.81
Comorbidities, n > 3, (%)	6 (32)	12 (41)	2 (9)	2	0.05
BMI, mean± SD	31 ± 6	32 ± 6	32 ± 8	2, 62	0.71
Medications, n (%)					
ACEI	16 (82)	21 (73)	16 (74)	2	0.45
Beta-Blocker	18 (95)	28 (96)	20 (96)	2	0.90
ARB	11 (60)	19 (64)	14 (69)	2	0.49
Diuretic	16 (84)	28 (95)	20 (95)	2	0.09
MoCA, mean ± SD	19 ± 3	21 ± 4	22 ± 3	2, 66	0.51
BDI, mean ± SD	9 ± 6	11 ± 9	12 ± 12	2, 53	0.52
Peak V02 kg/mL/min, mean ± SD	16 ± 4	16 ± 4	19 ± 6	2, 51	0.13
Duration on treadmill, min, mean ±	9 ± 5	7 ± 4	8 ± 4	2, 58	0.59
SD					
6MWT meters, mean ± SD	336 ± 85	359 ± 83	319 ± 86	2, 58	0.30

[a] = degrees of freedom of Chi-square (df) or ANOVA F-test (df1, df2) statistic;

[b] = of Chi-square tests of homogeneity for categorical characteristics or F-test in ANOVA for continuous characteristics.

Table 3.

Mean (standard error) outcome scores at baseline (BL), 3 and 6 months by treatment groups and results of the type III tests of fixed intervention effects (time × treatment interaction) from the mixed effect models.

Outcomes (M ±SE)#	UCAC (n=17)	Ex only (n=24)	Ex/CT (n=18)	Time x Group effect[1] F(df1, df2)	P value	Time x Group effect[2] F(df1, df2)	P value
Verbal Memory BL 3-months 6-months	−0.08 (0.20) −0.47 (0.21) −0.20 (0.21)	−0.08 (0.15) 0.14 (0.18) 0.07 (0.19)	0.18 (0.19) 0.37 (0.20) 0.25 (0.22)	4.34 (2, 53)	0.018	2.39 (4, 93)	0.056
Visual Memory BL 3-months 6-months	−0.09 (0.23) −0.21 (0.24) −0.90 (0.25)	−0.17 (0.18) 0.08 (0.21) −0.14 (0.23)	0.29 (0.22) 0.18 (0.24) 0.32 (0.26)	1.06 (2, 52)	0.355	0.61 (4, 93)	0.654
Processing Speed/ Attention BL 3-months 6-months	−0.09 (0.11) −0.09 (0.12) 0.20 (0.13)	−0.02 (0.10) 0.13 (0.11) −0.02 (0.12)	0.12 (0.11) −0.01 (0.13) −0.18 (0.14)	0.69 (2, 57)	0.506	2.85 (4, 98)	0.028
Working Memory BL 3-months 6-months	−0.04 (0.12) −0.03 (0.13) −0.15 (0.13)	0.09 (0.10) 0.12 (0.11) 0.10 (0.12)	−0.07 (0.12) −0.16 (0.13) −0.03 (0.14)	0.35 (2, 56)	0.710	0.55 (4, 96)	0.701
Reaction Time BL 3-months 6-months	0.14 (0.22) −0.05 (0.25) 0.02 (0.24)	0.11 (0.18) 0.07 (0.21) −0.13 (0.23)	0.29 (0.22) 0.18 (0.24) 0.30 (0.26)	1.54 (2, 37)	0.227	1.02 (4, 75)	0.404
PeakV02 mL/kg/min* BL 3-months	15.3 (1.3) 15.9 (1.3)	16.0 (1.0) 16.2 (1.0)	19.3 (1.1) 19.3 (1.2)	0.13 (2, 42)	0.877	NA	NA
6MWT (meters) BL 3-months 6-months	324.1 (19.2) 311.1 (20.0) 321.2 (20.2)	355.1 (15.9) 358.8 (16.9) 374.9 (18.7)	337.6 (18.5) 388.4 (20.2) 374.9 (20.6)	3.30 (2, 52)	0.045	2.08 (4, 94)	0.089
BDI-II BL 3-months 6-months	8.3 (2.0) 7.5 (2.0) 5.2 (2.1)	11.3 (1.6) 9.7 (1.7) 10.2 (1.8)	11.9 (1.9) 8.3 (2.1) 6.9 (2.1)	0.75 (2, 39)	0.479	1.14 (4, 76)	0.344

*only collected at BL and 3 months;

#adjusted for baseline comorbi dities.

[1]= Mixed effects model including two time points BL and 3 month.

[2]= Mixed effects model including all time points (BL, 3, 6 and 6 months).

Table 4:

Effect size estimates

Outcomes	Difference of change scores at 3 months* ($diff_{3M}$–$diff_{BL}$)	Cohen's *d*	Difference of change scores at 6 months& ($diff_{6M}$–$diff_{BL}$)	Cohen's *d*
Verbal memory				
Ex only vs UCAC	0.615	0.712	0.127	0.147
Ex/CT vs UCAC	0.586	0.678	0.194	0.224
Visual memory				
Ex only vs UCAC	0.356	0.356	0.021	0.021
Ex/CT vs UCAC	0.004	0.004	−0.002	−0.002
Processing Speed/Attention				
Ex only vs UCAC	−0.097	−0.199	−0.277	−0.568
Ex/CT vs UCAC	−0.201	−0.412	−0.592	−1.213
Working memory				
Ex only vs UCAC	0.079	0.149	0.131	0.247
Ex/CT vs UCAC	−0.065	−0.122	0.15	0.282
Reaction Time				
Ex only vs UCAC	0.096	0.109	0.019	0.022
Ex/CT vs UCAC	0.563	0.640	0.142	0.161
Peak V02 mL/kg/min+				
Ex only vs UCAC	−0.373	−0.077	-	-
Ex/CT vs UCAC	−0.611	−0.126	-	-
6MWT (meters)				
Ex only vs UCAC	16.79	0.198	22.72	0.268
Ex/CT vs UCAC	63.89	0.753	40.16	0.474
BDI-II				
Ex only vs UCAC	−0.844	−0.096	2.068	0.236
Ex/CT vs UCAC	−2.766	−0.316	−1.818	−0.208

+=Measured only at BL and 3 months.

*=Difference of mean differences between two treatment groups at 3 months;

&= Difference of mean differences between two treatment groups at 6 months. Cohen's *d* values of 0.20, 0.50, and 0.80 represent small, moderate and large effect