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Exercise-Based Cardiac Rehabilitation Improves Cognitive Function Among CVD Patients

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EXERCISE-BASED CARDIAC REHABILITATION IMPROVES COGNITIVE FUNCTION AMONG CVD PATIENTS

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“The only place where success comes before work is in the dictionary”
DEDICATION

Dedicated to the memory of my father, Terence, who was so proud of my achievements and always believed in my ability to be successful in the academic world.

You may be gone, but your unrelenting support and belief in me has made this journey possible.
Exercise-Based Cardiac Rehabilitation Improves Cognitive Function Among CVD Patients

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ABSTRACT

Objective: Investigate the effects of cardiac rehabilitation (CR) exercise training on cognitive performance and if the changes are associated with alterations in prefrontal cortex (PFC) oxygenation among patients with cardiovascular disease (CVD). Design: A single group pre-post design. Setting: An outpatient CR program. Subjects: Twenty (15 male, 5 female; mean (SD) age 64.8 (11.6) yrs) patients from an outpatient CR program. Intervention: At least 18 individualized CR sessions (approximately 6 weeks). Main measures: Pre- and post-CR changes in cognitive performance (a measure of 5
constructs from the NIH Fluid Cognition test battery), left-PFC and right-PFC activation (measured using functional near-infrared spectroscopy (fNIRS)) and cardiorespiratory capacity (measured by a submaximal graded treadmill test). **Results:** Patients showed improvements in cardiorespiratory capacity and various cognitive constructs (processing speed, attention, executive function, and working memory scores). A significant increase in PFC oxygenation, primarily in the left-PFC region, occurred at post-CR test. Correlation analyses revealed negative associations between changes in cognition (executive function and fluid composite score) and PFC changes. The change in cardiorespiratory capacity was positively associated with the change in working memory score. **Conclusions:** CVD patients enrolled in CR showed significant improvements in multiple cognitive domains along with increased cortical activation. The negative associations between cognitive functioning and PFC oxygenation suggest an improved neural efficiency, which is identified as higher cognitive performance for a given (or reduced) amount of cortical activation.
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SYMBOLS / ABBREVIATIONS

>: greater than
≥: greater than or equal to
<: less than
±: plus or minus
BDNF: brain-derived neurotrophic factor
BMI: body mass index
CAD: coronary artery disease
CBF: cerebral blood flow
CBT: cognitive behavioral therapy
cm: centimeters
CR: cardiac rehabilitation
CVD: cardiovascular disease
DLPFC: dorsolateral prefrontal cortex
DPF: differential pathlength factor
DSM5: diagnostic and statistical manual of mental disorders, 5th edition
fMRI: functional magnetic resonance imaging
fNIRS: functional near-infrared spectroscopy
Hbdiff: hemoglobin difference
HHb: deoxyhemoglobin
HR: heart rate
HRmax: maximum heart rate
HRR: heart rate reserve
HPA: hypothalamic-pituitary-adrenal
IGF-1: insulin-like growth factor-1
kg: kilogram
LPFC: left prefrontal cortex
m²: meters squared
MAP: mean arterial pressure
METs: metabolic equivalent of tasks
min: minute
O₂Hb: oxyhemoglobin
PFC: prefrontal cortex
RHI: reactive hyperemia index
RPE: rating of perceived exertion
RPFC: right prefrontal cortex
SD: standard deviation
tHb: total hemoglobin
TM: treadmill
TMT: trail-making test
VEGF: vascular endothelial growth factor
VO₂peak: peak oxygen consumption
VO₂max: maximal oxygen consumption
VT: ventilatory threshold
yrs: years
μmol: micromole
CHAPTER 1: INTRODUCTION

Cognitive impairment has been a well-established co-morbidity associated with cardiovascular disease (CVD) [1]. Patients diagnosed with multiple forms of CVD have demonstrated a decline across multiple cognitive constructs including executive function, memory, and psychomotor speed [2]. Vascular pathologies that lead to the development of heart disease are also considered major underlying factors to the development of stroke and vascular dementia [3]. These pathologies include coronary ischemia, hypertension, and dyslipidemia; therefore, the cognitive decline associated with CVD may be an early sign for later development of brain disorders [4]. According to the World Health Organization (WHO), approximately 50 million people have dementia, and there are nearly 10 million new cases each year [5]. In addition, Hebert et al. [6] state that the number of people in the US with dementia will increase dramatically in the next 40 years and is, therefore, considered a major health-care priority. Cardiovascular disease is also linked to anxiety and mood disorders which may manifest from CVD-related cognitive decline [7]. Both depression and cognitive decline have been observed among patients who underwent coronary bypass artery grafting procedures [8]. Moreover, up to 40% of individuals who have suffered a major cardiac event meet the criteria for major depressive disorder which presents a major barrier to treatment for CVD [9].

Although speculative, various mechanisms have been linked to cognitive dysfunction in patients with CVD; these mechanisms include poor aerobic fitness, endothelial dysfunction, CVD risk factors (e.g., hypertension, age), heart arrhythmias, and coronary bypass graft procedure [10-12]. It is suspected that these factors contribute to small reductions in cerebral blood flow (hypoperfusion) causing a lower energy state
and neuronal damage in localized brain regions associated with memory and learning [11]. The cognitive impairment as a result of chronic cerebral hypoperfusion among CVD patients is thought to be a consequence of neural degeneration and loss of neural plasticity [13]. Interestingly, cognition was restored when a pacemaker was implanted among patients who suffered from heart arrhythmias indicating the importance of normal cardiac functioning on brain health [14]. In addition, Tariff et al. [15] identified a genetic basis for cognitive decline among cardiac patients and discovered an association between the apolipoprotein E allele and short-term memory scores six weeks post cardiac operation.

Cognitive decline is also associated with disruption in the activation of the prefrontal cortex (PFC) region of the brain. The PFC has been identified as a key brain region responsible for cognitive control, goal-directed behavior, and is highly active during memory retrieval and periods of concentration [16]. The advancement of imaging technologies such as functional near infrared spectroscopy (fNIRS) and magnetic resonance imaging (MRI) have allowed researchers to observe PFC activation among those suspected of cognitive deficits to gain insight into neural mechanisms [17, 18]. Cognitively challenging tasks increase the demand on the PFC, and activation is observed by monitoring (using fNIRS) cerebral hemoglobin oxygenation changes for increases thereof which denote PFC activation [19]. Those with anxiety and mood disorders demonstrate diminished PFC activation during concentration tasks when compared to healthy counterparts [20]. A decrease in PFC oxygenation has been observed among cardiac patients who underwent cardiac bypass graft surgery; however, no assessment of PFC oxygenation changes has been measured among cardiac patients during cognitive
tasks [21]. In response to evidence that has linked cognitive decline to PFC oxygenation deficiency, it is suspected that the PFC may mediate cognitive decline that is associated with CVD.

Cardiac rehabilitation (CR) has been described as a program “that promotes secondary prevention of CVD and is an essential component of care for all cardiac patients” [22]. Specifically, phase II CR is an outpatient, exercise-based intervention which usually lasts 12 weeks in duration and forms a central element of the physical rehabilitation process. Besides exercise, a combination of additional therapies are provided in CR, including psychosocial support and risk factor education [23]. Cardiovascular improvements of CR include central hemodynamics (e.g., heart function), peripheral vasculature (e.g. endothelial function), and regulatory control (e.g., autonomic function), which all contribute to improvements in aerobic fitness [24]. Patients have further demonstrated heightened mood states (e.g., reductions in depression and anxiety), and positive behavioral changes (e.g., smoking cessation) [22]. The overall results of CR programs lasting from 6 to 12 weeks is an improvement in the patient’s quality of life [25-27]. Limited evidence has also suggested that cognitive improvements are a result of cardiac rehabilitation [10, 28-30]. Stanek et al. [10] found that CVD patients displayed improvements in multiple cognitive domains (global cognitive function, memory, and attention-executive-psychomotor) following a standard 12-week phase II CR program. Congestive heart failure patients improved in measures of attention and psychomotor speed after completion of a CR program [30]. It has also been shown that listening to music while exercising for an acute session can improve cognitive performance on a verbal fluency test in coronary artery disease (CAD) [31] patients enrolled in CR [29].
Gunstad et al. [28] also reported significant improvements in the Trail Making Test A and a digit Symbol-Coding test after a 12-week CR program. This limited evidence does suggest that exercise-based CR can improve cognitive performance in various domains among CVD patients.

The underlying mechanisms that explain the positive effect of exercise on cognitive function among cardiac patients are unclear. It is suspected that the primary component is an increase in central hemodynamics (e.g., cardiac output) during exercise, which drives an increase in brain blood flow velocity [32]. The transition from rest to low-intensity exercise increases cerebral blood flow and prefrontal cortex oxygenation [33]. Engaging in consistent aerobic exercise improves cerebral blood hemodynamics as demonstrated among heart failure patients who were found to have enhanced brain blood flow in the left prefrontal cortex (LPFC) region after a 12-week aerobic interval training program [34]. The delivery of blood and nutrients to the brain is thought to promote neurogenic mechanisms leading to global brain growth, and improvements in synaptic plasticity [35, 36]. Aerobic exercise training in elderly adults has also led to an increase in brain volume, which was associated with greater serum levels of brain-derived neurotrophic factor (BDNF) [31]. BDNF is a growth factor that supports the growth and health of brain glia cells [37]. Another possible mediator of exercise-related cognitive improvements is lactate production from the skeletal muscle. Increased lactate production provides evidence of increased metabolic flux and is believed to provide an alternative nutrient to glucose for brain astrocytes, and to serve as a precursor for glutamate release [38, 39]. Glutamate is the main excitatory neurotransmitter in the brain, and its excessive activation has been linked to learning and cognitive impairment in conditions of
psychosis and aging [40]. Lactate has also been linked to the induction of neural plasticity genes and further maintenance of long-term potentiation, a measure of memory and learning in animal studies [41, 42]. Animals that were injected with lactate demonstrated similar upregulation of brain plasticity markers as animals exercised at lactate threshold [43]. In summary, both the hemodynamic (cerebral oxygenation) response to, and metabolic stress of exercise are considered key components that explain exercise-related cognitive improvements.

Several key markers indicate changes in brain function and cognition in response to exercise training. Functional measures of the prefrontal cortex along with concentration assessments (measured by cognitive testing) are used in combination to determine if cortical activation mediates cognitive performance changes during mentally arduous tasks. More specifically, fNIRS recording of PFC activity is performed while the individual completes a series of cognitive tests. As previously stated, mentally challenging tests elicit activation in the PFC, and is identified using fNIRS by an increase in oxygenation changes, or oxygen extraction [44]. The use of this model allows researchers to observe if changes in PFC oxygenation (or activation) are linked to cognitive performance [45]. For example, those suffering from mood or psychological disorders have demonstrated lower PFC activation, which correlated with lower cognitive scores in comparison to healthy controls [46, 47]. Both enhanced PFC oxygenation change and cognitive improvements have been demonstrated after low-intensity aerobic exercise among both young and older adults [48-51]. A host of concentration tasks have been used to measure various cognitive constructs. In previous exercise-related studies, the Stroop and n-back tests have been used to measure processing speed, and memory
retrieval, respectively [52-54]. The NIH Toolbox is a validated test for measuring fluid cognition among adults, and includes the processing speed, memory, and overall executive function constructs [55]. The NIH Toolbox appears to be a more global assessment of cognition and may provide deeper insight into cognitive changes after exercise. In our previous work, we have demonstrated heightened PFC activation during NIH Toolbox administration after 45 minutes of moderate-intensity (70% of HRmax) aerobic exercise in human subjects (Moriarty et al., in submission).

Therefore, the present study seeks to prospectively evaluate if CR influences cognitive function among CVD patients. We further aim to explore if the improvements in various cognitive constructs (e.g., processing speed, memory, executive function) are associated with changes in PFC oxygenation (i.e., activation). Results may provide important insights into the mechanisms of how CR exercise interventions influence both cognition and brain activity, and further allow clinicians to identify appropriate exercise therapies for those suffering from CVD and cognitive dysfunction. Exploratory analyses will be conducted to investigate whether CR patients experienced improvements in cognitive function and to identify possible mechanisms for cognitive improvements, including changes in cardiovascular fitness and brain oxygenation.

The novelty of this study is the utilization of fNIRS brain imaging technology in observing PFC activation during cognitive testing pre- and post-CR. Upon completion of successful data collection, this will be first known study to report these results that will extend our understanding of the neurophysiological benefits of CR.
Problem Statement

Previous research has briefly described the positive cognitive performance changes in cardiac patients after completion of CR, yet there remains a gap in the literature to further clarify the underlying mechanisms. It has been shown that CR improves aerobic fitness; however, the specific adaptation (increased brain blood flow or tissue oxygenation) to long-term aerobic exercise that may explain any differences in cognitive performance or function is currently unknown. Furthermore, exploratory analyses will be conducted to examine whether CR participants experience improvements in cognitive function, and possible mechanisms for these changes, including changes in aerobic fitness parameters (e.g., increased estimated VO$_{2\text{peak}}$) and PFC oxygenation.

Purpose of the Study

The purposes of this current study are to: 1. Determine if exercise improves cognitive function among patients with CVD enrolled in CR; 2. Identify if cognitive changes are associated with changes in PFC oxygenation using fNIRS during cognitive testing; 3. Use exploratory analyses to identify if changes in functional capacity are associated with cognitive function (i.e., cognition and PFC activation) changes after 6 weeks of CR.

Limitations

The following limitations were identified in this study:

1. The study sample will consist of men and women with varying cardiac conditions who are enrolled in an outpatient CR program at New Heart Clinic, Albuquerque, NM. Therefore, the results of this study may not apply to individuals who are
healthy, have other chronic disease, or are outside of the range for age (18-85 years).

2. This study is a quasi-experimental design with no control group and thus results can only be compared from pre- to post-intervention time points within the CR group.

3. This study has no follow-up after the exercise-based intervention and, therefore, the long-term improvement in cognitive and/or PFC activation cannot be confirmed.

Assumptions

The following assumptions were identified in this study:

1. Prior to each pre- and post-intervention visit, each participant did not perform any vigorous exercise for 24 hours, did not ingest caffeine for 4 hours or alcohol for 12 hours, consumed the same small meal 2-3 hours prior, and consumed enough water to maintain adequate hydration.

2. Each participant completed all exercise sessions with good effort.

Hypotheses

The following hypotheses were tested in this study:

**Hypothesis 1**: When examining cognitive performance on the NIH toolbox test, CR patients will improve in fluid cognition following 6 weeks of an outpatient, exercise-based CR intervention.
It has been reported that 12 weeks of CR improved cognitive performance across multiple domains in patients with cardiovascular disease, suggesting that cognitive dysfunction is modifiable in this population [10, 29].

**Hypothesis 2**: Left and right PFC activation during cognitive testing will increase following 6 weeks of an outpatient, exercise-based CR intervention.

It has been reported that 6 months of aerobic exercise improved cerebral activation during cognitive testing among healthy older adults; however, to date, there has been no research on PFC activation during cognitive testing in response to an outpatient, exercise-based CR intervention [56].

**Scope of the Study**

Twenty male and female CR patients completed pre- and post-intervention cognitive and exercise testing to compare the cognitive performance (NIH toolbox) and PFC (oxygenation) responses prior to and following 6 weeks of an outpatient, exercise-based CR intervention. All PFC oxygenation measurements were collected continuously during pre- and post-intervention cognitive testing using the fNIRS device. All cognitive measurements were collected via the NIH Toolbox test.

**Significance of the Study**

The significance of the current study stems from the need to further investigate and identify the mechanisms of how cardiac rehabilitation may improve cognition among cardiac patients. Previous research has established that there is a direct link between CVD and neural disorders [57]. Since engaging in aerobic exercise has been shown to improve aerobic capacity and cognitive performance [58, 59], CR may serve as a treatment for not
only CVD, but also prevention for later development of neural disorders. The results of this study will contribute to the growing understanding of the global cognitive capacity and the neurophysiological mechanisms that underpin any adaptations following 6 weeks of CR.
Definitions

**Affective responses:** the emotional response to a situation.

**Attention:** the concentration of awareness on some phenomenon to the exclusion of other stimuli.

**Brain derived neurotrophic factor:** a protein that supports the survival of existing neurons, and encourages the growth and differentiation of new neurons.

**Cardiac output:** the volume of blood ejected from the left ventricle per minute.

**Cardiac rehabilitation:** a medically supervised program to improve cardiovascular health to reduce future heart problems.

**Cardiovascular disease:** a group of disorders of the heart and blood vessels.

**Cerebral hypoperfusion:** decreased brain blood flow.

**Coronary bypass artery graft:** a form of bypass surgery that can create new routes around narrowed and blocked coronary arteries.

**Coronary ischemia:** an inadequate blood supply to the coronary arteries.

**Deoxyhemoglobin:** the concentration of the form of hemoglobin without oxygen.

**Digit Symbol-Coding test:** an evaluation tool used to assess cognitive functioning.

**Episodic memory:** the memory of autobiographical events that can be explicitly stated or conjured.

**Executive function:** a set of processes related to managing oneself and one’s resources in order to achieve a goal (e.g., manage time).

**Functional near infrared spectroscopy:** is an optical non-invasive brain monitoring technology that measures changes in brain activity via changes in hemodynamic responses.
Hemoglobin difference: the concentration of oxygenated minus deoxygenated hemoglobin.

Memory: the structures and processes involved in the storage and subsequent retrieval of information.

Neurogenesis: the growth and development of nervous tissue.

Oxyhemoglobin: the concentration of the oxygen-loaded form of hemoglobin.

Processing speed: the speed in which a person can understand and react to the information they receive, whether it be auditory (language), visual (letters and numbers), or movement.

Psychomotor speed: an individual’s ability to detect and respond to rapid changes in the environment, such as the presence of a stimulus.

Prefrontal cortex: a part of the brain that makes up the frontal area of the frontal lobe.

Total hemoglobin: total hemoglobin concentration.

Trail Making Test Parts A and B: a neuropsychological test of visual attention and task switching.

VO$_{2\text{max}}$: the maximum amount of oxygen that an individual can utilize during intense or maximal exercise.
References


1. de La Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry Neurol* 2012; 2012.


CHAPTER 2: LITERATURE REVIEW

This chapter presents a review article, entitled “Acute Aerobic Exercise Based Cognitive and Motor Priming: Practical Applications and Mechanisms” which will be submitted for publication to the Journal of Motor Behavior. It is authored by Terence Moriarty, Christine Mermier, Len Kravitz, Ann Gibson, Nicholas Beltz, and Micah Zuhl. The manuscript follows the formatting guidelines of the journal. References and a figure are provided at the end of the manuscript.
Acute Aerobic Exercise Based Cognitive and Motor Priming: Practical Applications and Mechanisms

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ABSTRACT

Aerobic exercise priming involves acute exercise stimulation prior to one’s engagement in subsequent therapy or motor skill training. This concept is known as exercise priming and is a relatively new topic of research in the fields of exercise science and motor control. The authors report on physiological mechanisms that are related to the priming effect. In addition, parameters related to the exercise bout and the idea of combining exercise and therapeutic rehabilitation are explored. This exercise-based priming concept has the potential to be applied to many areas such as education, cognitive therapy, and motor rehabilitation.

Keywords: priming; exercise; cognition; motor; rehabilitation
1. Introduction

A lack of cardiovascular fitness has been linked with cognitive dysfunction and learning deficits in various clinical populations (Alosco et al., 2014; Katz et al., 2012); for this reason, recent research efforts have explored the benefits of aerobic exercise on brain health and cognitive functioning with positive results reported for both healthy and neurocognitively impaired individuals (Stoykov, Corcos, & Madhavan, 2017). Specifically, aerobic exercise has been shown to improve memory, processing speed and executive functioning among those with mental deficiencies (Altmann et al., 2016; Zhu et al., 2018). It also facilitates learning in healthy adults (Stern et al., 2019; Venckunas et al., 2016; Young, Angevaren, Rusted, & Tabet, 2015) and adolescents (Berse et al., 2015).

While it appears that aerobic exercise enhances cognitive abilities in humans, it is less well known if cognitive gains associated with exercise transfer into improved retention and learning outcomes that many therapeutic programs rely heavily upon. The level of cognitive functioning has been linked to outcomes in behavioral-based therapies for those being treated for substance abuse and mood disorders (Mohlman and Gorman, 2005; Sofuoglu, DeVito, Waters, & Carroll, 2013). Aerobic exercise may facilitate improvements in treatment outcomes (e.g., abstinence, anxiety, depression) through neural plasticity promoting mechanisms (e.g., increased brain flow and oxygenation). Further, cognitive performance components including information processing and memory may be of particular importance for motor skill acquisition in various rehabilitation programs (Taubert, Villringer, & Lehmann, 2015). Cortical activation through aerobic exercise may lead to downstream retention of motor skills taught during
physical therapy or sport coaching. This would be beneficial for stroke patients, athletes, and those with neuromuscular injuries. In this context, exercise may arouse areas of the brain that control memory, processing speed, and executive function that may support an individual to more fully engage in a cognitive or motor-based therapy. This concept has been defined as “exercise priming” and involves acute exercise stimulation prior to one’s engagement in therapy or motor skill training (Charalambous et al., 2018). In practice, performing a brief bout of aerobic exercise prior to cognitive or physical therapy, or before a practice session may lead to improvements in therapeutic or practical outcomes.

Efforts to understand the mechanisms of how aerobic exercise serves to enhance cognitive functioning is of vital importance to establish exercise as an adjunct treatment for various therapeutic or learning outcomes. Here, we focus on acute aerobic exercise and its priming effects on cognitive function, learning, and motor skill acquisition. For review papers on the benefits of aerobic, resistance, and combined aerobic and resistance exercise on cognitive performance, please see the reviews of Brunt, Albines, & Hopkins-Rosseel, (2019), Landrigan, Bell, Crowe, Clay, & Mirman, (2019), Smith et al. (2010), Wilke et al. (2019), and Zheng, Xia, Zhou, Tao, & Chen, (2016).

2. Mechanisms of Aerobic Exercise Priming

2.1 Brain Blood Flow and Oxygenation

Global brain blood flow remains relatively constant during acute aerobic exercise; although, there may be a shift in resources (i.e., oxygen consumption) from areas required for cognitive function to areas required for motor control and maintenance of vital function (e.g., blood pressure and thermoregulation) (Dietrich and Sparling, 2004; Ide and Secher, 2000). In specific cortical regions, blood flow and oxygenation (i.e.,
activation) are influenced by the intensity of the exercise bout. For example, activation in the prefrontal cortex (PFC), measured by brain oxygenation, increased during submaximal aerobic exercise (up to 80% of peak ability) but then decreased when intensity reached very hard or maximal effort (Rooks, Thom, McCully, & Dishman, 2010). The PFC is involved in executive function and cognitive control processes, and these illustrate that PFC activation is influenced by aerobic exercise intensity (Tempest, Eston, & Parfitt, 2014).

The relationship between the intensity of exercise and cognitive processes and psychological state can be explained by a theoretical framework called the dual-mode model (Ekkekakis, 2003) and the transient “hypofrontality” hypothesis (Dietrich, 2003, 2006). The dual-mode model proposes that affective responses (positive or negative) to exercise are regulated by the PFC and the regions of the brain that receive sensory input from the body (subcortical areas). During low to moderate exercise intensities (i.e., 60-70% of peak ability), the PFC works to maintain positive affective responses, while during higher intensities of exercise activation of the PFC becomes challenged by the upregulated and strong sensory stimuli from the body (Tempest et al., 2014). In agreement with this model, the transient “hypofrontality” hypothesis reveals that maintenance of cognitive and positive affective responses via PFC activation is challenged during high-intensity exercise due to a redistribution of metabolic resources to regions governing motor control. In support of these models, several research groups have reported a decrease in cortical oxygenation of the right PFC at exercise workloads above 80% of peak ability (Ando, Kokubu, Yamada, & Kimura, 2011; Bhambhani, Malik, & Mookerjee, 2007). High intensity and maximal effort exercise also appear to be
associated with reduced affective positivity when measured immediately post-exercise (Ekkekakis and Petruzzello, 1999). Therefore, during higher intensity exercise there is a shift in the metabolic activity of certain areas of the brain which may potentially lead to an overall negative-affective response (Dietrich, 2006). Conversely, exercising for 20 min at a moderate intensity (50% of peak ability) has been shown to significantly increase cerebral oxygenation during exercise (Tsubaki et al., 2018). These findings support the differential activation patterns of the PFC as the intensity of exercise increases.

Upon cessation of low-to-moderate intensity aerobic exercise, cerebral oxygenation remains elevated for up to 30 min (Faulkner, Lambrick, Kaufmann, & Stoner, 2016; Stavres, Gerhart, Kim, Glickman, & Seo, 2017; Tsubaki et al., 2018). Performing a cognitive task after exercise is potentially ideal as it takes advantage of the heightened cortical activity during recovery. Twenty to thirty minutes of moderate-intensity (45-60% VO$_{2\text{max}}$) cycling increased post-exercise cerebral oxygenation, which directly aligned with improvements in post-exercise executive function performance (Stroop task) (Stavres et al., 2017; Tsubaki et al., 2018). Yanagisawa et al. (2010) also reported an association between post-exercise cognitive performance and PFC oxygenation after a bout of moderate-intensity (50% VO$_{2\text{peak}}$) exercise. Increased PFC activation may be indicative of higher cortical activity and, therefore, greater mental effort. However, McKendrick, Ayaz, Olmstead, & Parasuraman (2014) found a negative association between verbal working memory performance and bilateral ventrolateral PFC activation in response to 5 consecutive days of a cognitive training intervention. The authors interpreted these data as increased neural efficiency, more specifically defined as
reduced mental workload for mental processing, and increased working memory capacity with cognitive training (McKendrick et al., 2014). Similarly, Hsu et al. (2018) reported that a 6-month aerobic training intervention reduces activation in the left lateral occipital cortex and right superior temporal gyrus, and this reduced activity is associated with improved Flanker task performance (response inhibition). The findings from these studies suggest that improved neural efficiency may underlie the effect of aerobic or cognitive exercise on cognitive function. Thus, changes in PFC hemodynamics following aerobic exercise may be useful in clinical populations for retaining and/or improving neural performance in cognitive and therapy-based skills.

While the bulk of the evidence supports low-to-moderate intensity exercise as a means of increasing post-exercise cerebral oxygenation, limited data have also demonstrated an increase in post-exercise cortical activity following short-duration, high-intensity exercise. Bediz et al. (2016) found that an acute (30 seconds) supramaximal cycling bout increased PFC oxygenation during a post-exercise cognitive task. Despite the increase in PFC oxygenation, there were no significant differences in post-exercise cognitive test (2-Back) scores as compared to pre-exercise. Perhaps high-intensity exercise causes increased fatigue thereby requiring the participants to work harder to activate the PFC (evidenced by increased PFC oxygenation) to maintain cognitive performance during the post-exercise test as compared to pre-exercise. Further, higher cortical activation with no change in cognitive performance may indicate worsening neural efficiency as it takes more neural input for a given output. Conversely, an increase in both mental performance and PFC activation has been reported after short duration high intensity exercise (Kujach et al., 2018). For example, Kujach et al. (2018) found that
10-min of high-intensity intermittent exercise increased cortical activation in the left-dorsal-lateral prefrontal cortex (LDPFC), which corresponded with improved executive function. Possible explanations for the differing responses include, the specific cognitive test chosen, the high exercise intensity protocol, and the time at which the cognitive test was administered.

Evidence suggests that cerebral blood flow rises during low- to moderate-intensity exercise; this appears to translate to post-exercise elevation in PFC activity. The heightened activation in PFC after exercise may help to explain how acute exercise influences cognitive functioning.

2.2 Growth and Neurotrophic Factors

Another mechanism that may explain exercise related gains in cognitive function is the production and release of neurotrophic growth factors which promote neurogenesis and plasticity in the various regions of the brain. Identified neurotrophins include insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), all of which have been shown to be upregulated after various types of physical exercise (Heisz et al., 2017; Maass et al., 2016).

Vascular endothelial growth factor is a well-known growth factor and an important signaling molecule involved in angiogenesis and vasculogenesis (Amaral, Papanek, & Greene, 2001; Lee and Son, 2009). Interestingly, VEGF-A, which is a gene from the VEGF family, increases following either high-intensity exercise or a lactate injection among C57BL/6 mice (Lezi, Lu, Selfridge, Burns, & Swerdlow, 2013). Gustafsson, Puntschart, Kaijser, Jansson, and Sundberg (1999) also reported that a single bout of dynamic exercise increases VEGF and that there is a graded response in VEGF
directly related to the metabolic stress of exercise in humans. Therefore, it has been proposed that the VEGF response is due to lactate production during exercise. Morland et al. (2017) suggested that activation of the lactate receptor (HCAR1) in the brain enhances the effect of VEGF-A and brain angiogenesis, thereby providing a link between aerobic exercise and brain nourishment. During and post-exercise, lactate released from the contracting skeletal muscle is able to cross the blood-brain barrier and be metabolized by the human brain (Dalsgaard, 2006). Lactate has also been linked with promoting the expression of plasticity genes and being required for long-term memory formation and processing (Newman, Korol, & Gold, 2011; Suzuki et al., 2011; Yang et al., 2014). Moreover, intravenous infusion of 100mM L-lactate has been shown to ameliorate cognitive impairment in rats that had traumatic brain injury (Holloway et al., 2007). Since brain dysfunctions are associated with hypoperfusion and vascular complications, lactate release as a result of exercise may facilitate VEGF expression and act as a potential mechanism for treatment against cognitive decline and other brain conditions.

In addition, IGF-1 has been shown to be involved in the modulation of BDNF which is emerging as a key mediator of synaptic plasticity in the memory center of the brain, the hippocampus (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006). At the cellular level, increases in BDNF may be the link between exercise and learning; although this relationship is somewhat controversial and not very well understood (Charalambous et al., 2018). BDNF is thought to regulate synaptic proteins (e.g., synapsin I and synaptophysin) within the hippocampus thereby improving axonal branching and allowing for an increased effectiveness in synaptic transmission (Danzer, Crooks, Lo, & McNamara, 2002; Vaynman, Ying, & Gomez-Pinilla, 2004). Korte et al.
(1995) blocked the expression of BDNF in mice and found them to have a significantly reduced long-term potentiation (a measure of synaptic plasticity). Heldt, Stanek, Chhatwal, and Ressler (2007) found that BDNF deletion from the hippocampus impaired novel object recognition and spatial learning in mice. Importantly, these impairments are reversed when exogenous BDNF is given to a BDNF-deficient animal, further providing support for the importance of this neurotrophic factor in neural and cognitive function (Cotman and Berchtold, 2002).

The link between BDNF deficiency and cognitive impairment may be remedied by upregulation of this neurotrophin via aerobic exercise. Acute exercise induces BDNF expression in brain regions of rodents, and it appears to be both exercise intensity and dose dependent. For example, de Almeida et al. (2013) found that rats that performed high intensity exercise had elevated hippocampal expression of BDNF in comparison to non-exercise control rats. In addition, Adlard, Perreau, Engesser-Cesar, and Cotman (2004) found that animals that ran greater distances than their littermates in wheel running activity had higher levels of BDNF protein in the hippocampus.

In humans, serum BDNF is commonly measured as an indirect indicator of neurogenesis. This is based on evidence that BDNF produced in the brain accounts for 70-80% of circulating BDNF in response to aerobic exercise in humans (Rasmussen et al., 2009). The increase in serum BDNF has been reported in response to acute bouts of aerobic exercise and also linked with better hippocampal function (Griffin et al., 2011). The magnitude of the increase in serum BDNF in humans may be exercise intensity dependent. Ferris, Williams, and Shen (2007) found that BDNF levels increase by 13% following cycling at an intensity above the ventilatory threshold and by 30% following a
graded exercise test to volitional fatigue. More recently, Ross, Saladin, George, and Gregory (2019) reported a direct linear relationship between exercise intensity and post-exercise serum BDNF among both healthy and moderately depressed individuals. The intensity-dependent increase in serum BDNF has also been positively associated with improved prefrontal cognitive functioning in humans (Hwang et al., 2016). The connection between exercise, BDNF, and cognition is thought to be through a common single-nucleotide polymorphism of BDNF, Val66Met, which has been associated with cognitive deficits in those with Parkinson’s Disease (Guerini et al., 2009) and with reduced hippocampal volume in healthy subjects (Bueller et al., 2006). These data indicate that acute aerobic exercise can improve cognitive function concomitant with increased BDNF concentrations, thereby suggesting a functional role for this neurotrophic factor in acute exercise-induced cognitive enhancement in humans.

In summary, the production and release of neurotrophins, mainly VEGF and BDNF, in response to acute aerobic exercise, are linked to cognitive performance improvements.

2.3 Myokines and Hormones

Contracting skeletal muscles release myokines that work to regulate whole body metabolism as well as maintain functional and structural properties of the muscle itself (Kim et al., 2019). A relatively new myokine which was discovered in 2012, irisin, serves as a neuroprotective agent, and reportedly attenuates brain damage incurred during various types of cerebral insult (ischemia, stroke) (Asadi, Gorjipour, Behrouzifar, & Vakili, 2018). Exercise-induced release of irisin functions via activation of Akt and ERK1/2 pro-survival signaling pathways thereby reducing ischemia-induced neuronal
injury. Due to irisin’s influential role on metabolism, it was suggested that this myokine may link metabolism and cardio-cerebrovascular diseases (Li, Li, Yuan, Qu, & Wang, 2017). In addition, endurance exercise increases the expression of FNDC5 (a membrane protein that is cleaved and secreted as irisin) which induces upregulation of BDNF in the hippocampus, thus having a positive impact on potential neuronal growth (Wrann et al., 2013). Cathepsin B is another recently identified myokine that is important for neural plasticity and cognitive function (Moon et al., 2016). Aerobic exercise has been shown to increase Cathepsin B plasma levels in mice, monkeys, and humans (Moon et al., 2016). In humans, changes in Cathepsin B positively correlated with fitness and memory (Moon et al., 2016). Though, to date, little research has been conducted on myokines’ effect on the brain; however, both irisin and Cathepsin B may play important roles in the beneficial effects of exercise on brain health and function.

Exercise also acts as a physiological stressor which activates the hypothalamic-pituitary-adrenal (HPA) axis and increases the secretion of cortisol, also known as a “stress hormone”. It has been proposed that exercise training promotes stress coping and cognitive function via a more rapid cortisol release (shorter time to peak cortisol levels), and a decrease in secretion. For example, women who completed a 3-month intensive yoga program had significant improvements in measures of stress and psychological outcomes, in addition to decreased cortisol levels after participation in a single yoga class (Michalsen et al., 2005). It has also been shown that exogenous oral administration of cortisol reduces anxiety-driven selective attention to threat (Putman, Hermans, Koppeschaar, Van Schijndel, & Van Honk, 2007). Cortisol acts through the glucocorticoid receptors and upregulates medial prefrontal cortex dopamine levels; this
ultimately allows one to better control and cope with stressors (e.g., physical and mental) (Chen et al., 2017). These results suggest that exercise may act as a buffer to cortisol secretion. Thus, it is important to note that cortisol may be a marker of initial stress while dopamine levels may better reflect the effectiveness of stress coping (Chen et al., 2017). This stress coping mechanism has important clinical implications for those clinically depressed or with symptoms of anxiety. Increased dopamine may ameliorate negative symptoms associated with depression and anxiety, allowing them to perform better during cognitive or motor skill therapy following an acute exercise bout. Exercise has the capacity to influence the HPA axis allowing for better stress coping abilities and improved cognitive function.

In summary, acute aerobic exercise appears to promote cognitive gains which may, in part, be mediated through cerebral blood flow and cortical activation, growth and neurotrophic factors, as well as several myokines and hormones. For this reason, researchers are beginning to examine the role of exercise as a cognition-stimulating mechanism to improve cognitive performance and enhance motor skill acquisition in both healthy and clinical populations (Lefferts, DeBlois, White, & Heffernan, 2019).

3. Acute Aerobic Exercise as a Priming Technique for Cognitive Improvements and Motor Skill Acquisition

“Exercise priming” refers to a non-conscious process that promotes cognitive or motor skill related learning, whereby performing an acute exercise bout alters the response of another stimulus (Stoykov et al., 2017). Priming relies on the transient cognitive benefits of acute aerobic exercise and, when strategically performed before or after a task (either motor or cognitive), may improve learning and retention outcomes. In humans,
commonly studied cognitive domains include information processing, reaction time, memory, executive functioning, and attention (Chang, Labban, Gapin, & Etnier, 2012). Typical study protocols include a baseline measurement of the specific cognitive domain(s) or motor task of interest followed by an acute aerobic exercise session and then retesting of the cognitive domain(s) or motor task. Acute bouts of aerobic exercise ranging from 10-30 min at an intensity of 40-100% of maximal intensity have stimulated improvements in various cognitive domains and motor tasks.

For example, young adults demonstrated improved reaction times after performing acute moderate-intensity (50-70% of maximal heart rate) exercise for 20-30 min (Harveson et al., 2016; Sibley, Etnier, & Le Masurier, 2006; Wang et al., 2019). Enhanced post-exercise cognitive performance was linked to heightened activation in the prefrontal cortex region of the brain (Endo et al., 2013). Similarly, activation of the PFC and improvements in reaction time have been reported among older individuals after 10 min of moderate-intensity exercise at 50% VO$_{2\text{max}}$ (Hyodo et al., 2012; Lucas et al., 2012). Cognitive improvements have also been reported among clinical populations (e.g., patients with Multiple Sclerosis, depression, breast cancer) after acute bouts of moderate-intensity activity (Salerno, Rowland, Kramer, & McAuley, 2019; Sandroff, Hillman, Benedict, & Motl, 2015; Vasques, Moraes, Silveira, Deslandes, & Laks, 2011). Recently, Lefferts et al. (2019) found that a 30-min bout of moderate-intensity cycling decreased reaction time in the Flanker and memory recognition tasks in middle-aged individuals with hypertension. Support for the “priming” effect on behavioral performance has also been illustrated in post-stroke patients following an acute 15-min bout of cycling as reported by an improvement in the behavioral performance of a working memory task.
compared with the non-exercise control condition (Moriya, Aoki, & Sakatani, 2016). These results demonstrate that bouts of acute exercise support cognitive improvements among young and older adults, along with clinical populations.

Acute exercise has also been linked to enhanced motor skill performance. Several research groups have shown that performing a 30-min bout of moderate-intensity (60% - 85% of maximal heart rate) exercise prior to a motor skill task improves motor skill acquisition among healthy adults (Snow et al., 2016; Statton, Encarnacion, Celnik, & Bastian, 2015). Hubner, Godde, & Voelcker-Rehage (2018) found that an acute 25-min bout of moderate-intensity cycling (60% of participants max watts) in older adults improved performance in a fine motor task and enhanced activity at the contralateral frontal region. It was suggested that acute exercise facilitated motor compensation processes typically characterized by activation in alternative brain areas (Levin, Kleim, & Wolf, 2009). Short duration (15-20 min), higher-intensity exercise has also been linked to improved motor skill retention (Dal Maso, Desormeau, Boudrias, & Roig, 2018; Mang, Snow, Campbell, Ross, & Boyd, 2014; Mang, Snow, Wadden, Campbell, & Boyd, 2016; Roig, Skriver, Lundbye-Jensen, Kiens, & Nielsen, 2012; Skriver et al., 2014; Stavrinos and Coxon, 2017). For example, Mang et al. (2014, 2016) found that 20 minutes of high-intensity interval cycling (3-min work bout at 90% VO_{2peak} alternating with 3-min recovery) performed prior to motor skill practice, improved skill retention in response to a 24-hour delayed retention test. The authors suggested the improvement occurs as a result of an increased rate of motor memory retrieval and promotion of sequence-specific implicit motor learning (Mang et al., 2014; Mang et al., 2016). Similarly, interval cycling led to better retention of a motor skill at the 24-hours and 7-days follow-up compared to a
non-exercise control (Skriver et al., 2014). Roig et al. (2012) also showed a significantly better retention of a motor skill at 24 hours and 7 days after an acute bout of high-intensity exercise performed either before or after visuomotor accuracy-tracking practice. Interestingly, the group that exercised after the practice showed a better retention of the skill at 7 days. Others are in agreement with these findings; the effects of exercise performed after practicing a motor task are beneficial for retention of that particular task (Dal Maso et al., 2018; Stavrinos and Coxon, 2017).

While high-intensity exercise has shown to be effective for enhancing motor skill retention among healthy adults, less intense exercise (60-70% of maximum capacity) appears to be more beneficial among clinical populations. For example, Steib et al. (2018) reported that a single 30-min bout of aerobic moderate intensity cycling significantly improved motor skill acquisition of a novel balance task in a 24-hour skill retention test compared to the control condition among Parkinson’s patients. One 20-min session of treadmill walking (at 70% of maximal heart rate) also improved subsequent skilled movement of the hemiplegic upper extremity in individuals with chronic stroke (Ploughman, McCarthy, Bossé, Sullivan, & Corbett, 2008). These data represent a beneficial starting point for describing the appropriate exercise stimulus among clinical populations.

The evidence presented above suggests that acute exercise positioned proximal to (before or after) cognitive or motor tasks improves performance on subsequent tasks (see figure 1). Further, long-term moderate-intensity aerobic exercise programs ranging from 6 weeks to six months have produced positive outcomes on cognitive function and motor skill retention (Amjad et al., 2019; Cruise et al., 2011; Duchesne et al., 2015; Maass et
al., 2015; Quaney et al., 2009; Sandroff et al., 2016; Song and Yu, 2019; Stern et al., 2019; Uc et al., 2014). These results have been documented among healthy individuals along with those suffering from cognitive and motor impairment. Based on these data, exercise may serve as an adjunctive therapy to cognitive or motor (i.e., physical) therapies. Examples include an aerobic exercise program designed to operate alongside cognitive behavioral therapy (CBT) for treatment of substance use disorder or severe depression or an aerobic exercise program in conjunction with physical therapy for stroke patients. Cognitive deficits are mechanistic underpinnings of brain and behavioral disorders (Uhlhaas and Singer, 2006). The cognitive or motor function improvements induced by exercise may “prime” the patient to more fully engage in and benefit from therapeutic tasks for various treatments. Limited efforts have been made to partner exercise with therapy; whereas, the bulk of research has examined “treatment as usual”, comparing exercise alone to therapy (Stathopoulou, Powers, Berry, Smits, & Otto, 2006; Zschucke, Gaudlitz, & Ströhle, 2013). We argue that exercise cannot replace cognitive or motor therapy but may be able to enhance the benefits. For example, exercise combined with cognitive therapy for the treatment of schizophrenia improved symptoms and functional outcomes compared to cognitive therapy alone (Malchow et al., 2016; Nuechterlein et al., 2016). In addition, stimulant users report more abstinent days when they participate in exercise combined with therapy compared to therapy partnered with health education (Trivedi et al., 2017). Similarly, Gulf War Veterans who experienced multisymptomatic illnesses and participated in an exercise program combined with a CBT intervention were 1.72 times more likely to report improvements in functional outcomes compared to usual care (Donta et al., 2003). Mixed results for the benefit of
exercise combined with behavioral treatment have been reported among mood disorder patients. McEntee and Halgin (1999) reported similar improvements in anxiety among adults who participated in CBT alone, exercise alone, or CBT plus exercise; however, no differences were reported between groups. Comparable results have been reported among depressed adults who participated in either cognitive therapy or therapy combined with exercise (Veale et al., 1992). Although both groups improved, no between-group differences were detected. Several factors may explain the null findings for this population. First, the severity of mood disorder may influence outcomes. Those with more severe depression or anxiety may experience heightened cognitive impairment; therefore, combination therapy (exercise plus CBT) may be more beneficial for them (McDermott and Ebmeier, 2009). Second, exercise adherence plays a role; higher exercise compliance is associated with a greater reduction of symptoms of depression and anxiety (Herring, O’Connor, & Dishman, 2010). Mood disorder patients are traditionally noncompliant to health-related treatments (DiMatteo, Lepper, & Croghan, 2000). Third, exercise alone appears to be as effective for mood disorder states, and, therefore, exercise may serve as a primary treatment as opposed to an adjunctive therapy.

In summary, both acute and chronic exercise training studies have provided initial evidence that aerobic exercise improves cognitive and motor function in cognitively impaired individuals. Specifically, the cognitive benefits associated with such exercise interventions have been shown to extend beyond improving mobility of limbs to also improving sensorimotor learning and performance in cognitive tasks. Therefore, aerobic exercise in combination with therapeutic recovery and motor control rehabilitation techniques may ultimately augment functional outcomes through cognitive effects. As the
number of individuals with cognitive and motor impairments continue to rise, it is
imperative that more research is conducted in this area to define the specific parameters
(e.g., intensity, duration) and combinations (e.g., exercise and therapy) of such chronic
exercise interventions.

4. Conclusions

Aerobic exercise, both acute and chronic, has the ability to prime the brain for both
cognitive and motor task performance. These findings provide a stable groundwork for
designing and prescribing acute aerobic exercise in future research studies examining the
effects of exercise on cognitive performance and motor skill acquisition. Applying this
priming idea to education, rehabilitation, and therapy has the potential for improved
cognitive and motor performance and may form an important component of
improvements in these fields [Figure 1 near here]. Finally, the combination of exercise
and various forms of therapeutic rehabilitation may enhance the functional outcomes and
quality of life for individuals with cognitive or motor impairments and perhaps be the
way of the future with further in-depth research and knowledge of mechanisms.
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Figure 1. Using an acute aerobic exercise bout to prime cognitive and motor performance. Performing an acute aerobic exercise session immediately before cognitive and motor training may facilitate improvements in cognitive and motor function by capitalizing on aerobic exercise–induced increases in the capacity for neuroplasticity. CBF=cerebral blood flow.
CHAPTER 3: RESEARCH MANUSCRIPT

This chapter presents a research manuscript, entitled “Exercise-Based Cardiac Rehabilitation Improves Cognitive Function Among CVD Patients”. This manuscript is authored by Terence Moriarty, Kelsey Bourbeau, Christine Mermier, Len Kravitz, Ann Gibson, Nicholas Beltz, Omar Negrete and Micah Zuhl. The manuscript will be submitted to the *Clinical Rehabilitation Journal* and follows the formatting and style guidelines of this Journal. References are provided at the end of the chapter. Figures and Tables are provided after the references.
Exercise-Based Cardiac Rehabilitation Improves Cognitive Function Among CVD Patients

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ABSTRACT

Objective: Investigate the effects of cardiac rehabilitation (CR) exercise training on cognitive performance and if the changes are associated with alterations in prefrontal cortex (PFC) oxygenation among patients with cardiovascular disease (CVD). Design: A single group pre-post design. Setting: An outpatient CR program. Subjects: Twenty (15 male, 5 female; mean (SD) age 64.8 (11.6) yrs) patients from an outpatient CR program. Intervention: At least 18 individualized CR sessions (approximately 6 weeks). Main measures: Pre- and post-CR changes in cognitive performance (a measure of 5 constructs from the NIH Fluid Cognition test battery), left-PFC and right-PFC activation (measured using functional near-infrared spectroscopy (fNIRS)) and cardiorespiratory capacity (measured by a submaximal graded treadmill test). Results: Patients showed improvements in cardiorespiratory capacity and various cognitive constructs (processing speed, attention, executive function, and working memory scores). A significant increase in PFC oxygenation, primarily in the left-PFC region, occurred at post-CR test. Correlation analyses revealed negative associations between changes in cognition (executive function and fluid composite score) and PFC changes. The change in cardiorespiratory capacity was positively associated with the change in working memory score. Conclusions: CVD patients enrolled in CR showed significant improvements in multiple cognitive domains along with increased cortical activation. The negative associations between cognitive functioning and PFC oxygenation suggest an improved neural efficiency, which is identified as higher cognitive performance for a given (or reduced) amount of cortical activation.
INTRODUCTION

Cardiovascular disease (CVD) remained the leading cause of death in the United States (>800,000 deaths/year), with an estimated annual cost of $351.2 billion in 2014-15 [1, 2]. An under recognized yet important symptom of CVD is cognitive impairment; whereas, cardiac patients demonstrate deficits in various cognitive domains with particular difficulty in tasks related to executive function and psychomotor speed [3]. For example, Gharacholou et al. [4] reported mild to severe cognitive impairment among nearly 30% of acute myocardial infarction survivors. The importance of cognitive performance in those with CVD lies in the fact that cognitive dysfunction is related to poorer outcomes in cardiac rehabilitation [5], heightened risk for the development of dementia and Alzheimer’s disease [6], physical disability [7], reduced health quality of life [8], higher rates of early hospital re-admissions [9], and increased mortality [10]. Although the exact mechanisms remain unknown, research suggests that cerebral hypoperfusion and reduced cardiac output most likely contribute to the cognitive impairments observed in individuals with CVD [11, 12]. However, other comorbidities may also play a role in the development of cognitive dysfunction in this population, such as age, hypertension, history of myocardial infarction, and diabetes [4, 13, 14].

Cardiac rehabilitation (CR) is a standard treatment for CVD patients and has been shown to be beneficial for both cardiovascular health and cognition among patients who participate [15, 16]. Specifically, CR interventions have been associated with improvements in global cognitive abilities, memory, psychomotor speed, and complex attention [15, 16]. Programs are typically aerobic exercise-based and range between 12-36 sessions [16-19]. Given these findings, there is reason to believe that participation in
CR may improve multiple cognitive domains. However, the specific mechanisms that lead to cognitive improvements among CVD patients enrolled in CR are unknown.

Mentally demanding tasks require greater neural input which increases oxygen demand and, thus, metabolic activity of cortical areas [20]. Cognitive impairment among CVD patients is believed to be a result of vascular pathologies leading to possible cerebrovascular dysfunction [21]. Those with hemodynamic insufficiencies (e.g., cardiac patients) may be unable to meet the heightened oxygen requirements of cortical areas involved in various cognitive processes [22]. Therefore, one proposed process that explains how exercise-based CR leads to improvements in cognitive function is through enhanced central hemodynamics (heart and blood pressure regulation) and changes in cerebral oxygenation [23]. An increase in cardiac output among heart failure patients as a result of CR was linked with heightened cortical oxygen delivery [24] and improvements in psychomotor speed and attention [25]. Exercise training that leads to improvements in functional capacity (i.e., maximal aerobic capacity or $\text{VO}_2\text{max}$) modulates brain oxygenation and neuronal activity during concentration-related tasks which lead to overall improvements in cognitive function [26-28].

The primary cortical site that is monitored during cognitive assessments is the prefrontal cortex (PFC). The PFC houses executive processes that affect various areas of cognitive function including, but not limited to, information processing, attention, and working memory [29]. PFC activity is commonly monitored by measuring oxygenation changes; heightened oxygenation occurs during mentally challenging tasks [30]. During the last decade, researchers have used functional near-infrared spectroscopy (fNIRS) extensively to measure cerebral oxygenation and blood flow responses to cognitive
stimulation and exercise in various regions of the brain including the PFC [31, 32]. The advantages of using fNIRS is that it is portable, non-invasive, and provides information regarding physiological changes associated with brain activity [33, 34]. This method of quantifying physiologic changes in the brain has also been used during cognitive tasks and dynamic exercise in a CVD population [24, 35, 36]. An increase in brain activity initiated by a cognitive task results in an increase in cerebral blood flow (CBF) and neuronal oxygen delivery in order to meet the increased demand for oxygen and nutrients. Thus, neuronal activation during a series of cognitive tasks elicits an increase in arterial oxygen content (oxyhemoglobin, O$_2$Hb) and total hemoglobin (tHb) with a decrease in the fractional oxygen utilization (deoxyhemoglobin, HHb) [26, 37].

The effect of chronic exercise training on PFC oxygenation during cognitively demanding tasks is not well understood. In a review by Brehmer et al. [38], it was noted that changes in brain activation following exercise training programs are equivocal. Chronic exercise training studies (4-12 months in duration) have shown both increased and decreased PFC activation in older adults [26-28]. For example, Coetsee and Terblanche [26] found that older adults who performed 16 weeks of moderate-intensity exercise demonstrated decreased brain oxygenation, or activation, during a mental task. Reduced neural activity in response to a similar cognitive task is thought to be evidence of an increase in neural efficiency [39]. Conversely, higher levels of physical activity correlated with greater prefrontal oxygen availability and cognitive inhibitory control among a cohort of healthy adults [40]. Investigations into the change in PFC responses following aerobic exercise interventions in clinical populations will add to the published literature in this area.
While the effect of cardiac rehabilitation on cognitive function among CVD patients has been briefly explored, less well known is the role of cortical oxygenation changes in response to CR. This analysis would provide insight into possible mechanisms by which CR influences cognitive function. Thus, the primary aims of this investigation were to determine if 6 weeks of CR exercise training improves cognitive performance and if these changes are associated with PFC oxygenation changes during cognitive tasks.

METHODS

2.1 Subjects

Patients from an outpatient CR program in Albuquerque, NM were enrolled. Individuals with a history of myocardial infarction, stable angina pectoris, heart valve repair or replacement, percutaneous coronary intervention, coronary artery bypass graft, heart failure, and/or coronary artery disease (CAD) who were proficient in the English language and under the age of 85 years were eligible to participate. Patients were excluded if they had any of the following: 1) history of psychiatric illness, 2) history of neurologic brain disease, or 3) age > 85 years. Patients were not excluded on the basis of history of major depression, provided that it had been effectively treated. Upon meeting study criteria, patients were provided an informed consent document to review; their written signature confirmed enrollment in the study. A total of 28 patients enrolled in the study; however, 8 individuals did not complete follow-up cognitive assessment, leaving a sample of 20 participants who completed both pre- and post-CR cognitive evaluations and were eligible for primary analyses of CR-related cognitive improvements (15 males and 5 females) (Table 1). The University of New Mexico Institutional Review Board
approved all methods (approval number 19218) and all individuals provided written informed consent before participating in this study. All research methods were carried out in accordance with the Declaration of Helsinki.

[insert Table 1.]

### 2.2 Study Protocol

Each patient completed anthropometric, cognitive, and submaximal exercise evaluations on separate occasions before and again upon completion of 18 CR sessions (approximately 6 weeks later). The fNIRS was used to measure PFC oxygenation during the cognitive evaluation. Upon enrollment in CR, patients were scheduled for an initial consultation with a cardiologist and clinical exercise physiologist. After their intake meetings, consenting patients were fitted with the fNIRS cap and completed cognitive testing followed by a submaximal exercise estimation of peak functional capacity (in METs) [41]. Post-testing was scheduled within one week of completing the 18th CR exercise session (approximately 6 weeks after pre-testing). The same procedures were completed at follow-up testing, including physician consultation, cognitive testing (with fNIRS cap), and exercise evaluation. If participants were unable to complete the cognitive test prior to the submaximal exercise test on the same day (due to scheduling conflicts), the cognitive test was scheduled within three days of the submaximal exercise test, similar to the pre-testing protocol. All pre- and post-CR-testing were completed at approximately the same time of day to minimize circadian rhythm influences on cognition or exercise performance [42, 43]. An outline of the study protocol is shown in Figure 1.
2.3 Cardiac Rehabilitation Program

Participants were enrolled in the phase II CR program at an outpatient rehabilitation clinic in Albuquerque, New Mexico. The program is a medically supervised intervention based on the American Heart Association guidelines [44]. Participants are encouraged to attend rehabilitation sessions three times per week with each exercise session prescribed at an intensity of 50-80% heart rate reserve (HRR) or rating of perceived exertion (RPE) of 3-5 (moderate to hard intensity, 0-10 scale) [45]. Each individualized CR session consisted of approximately 30-60 mins of aerobic exercise, dependent upon the patient’s initial aerobic fitness level; the weekly volume of exercise was progressively increased throughout CR. Customized exercise plans were developed for each patient and consisted of a warm-up, cooldown, stretching, and a main aerobic exercise phase utilizing various exercise modalities (e.g., rowers, treadmills, stationary cycles, elliptical trainers, arm ergometer). Education classes were also offered to the patients. These classes are designed to promote positive lifestyle changes through nutrition and exercise and to increase patients’ understanding of heart conditions and risk factor reduction. Attendance of the CR exercise sessions, but not the education classes, was tracked by the researchers.

2.4 Functional Near Infrared Spectroscopy (fNIRS) Recording

A dual wavelength (760 and 850 nm), light weight (230g), portable cerebral fNIRS device (OctaMon, Artinis Medical Systems, Elst, The Netherlands) was used to
evaluate PFC oxygenation. This measurement was evaluated at intake and after 18 sessions of CR during the cognitive assessment. The portable unit consisted of a headband with 8 optodes and 2 receivers, with an interoptode distance of 3.5 cm. Four LED optodes (transmitters) combined with one receiver were placed over the right and left prefrontal cortex regions (RPFC and LPFC, respectively) (4 x 2 configuration). The configuration created a total of 8 channels. Optode placement was based on the modified international electroencephalogram 10-20 system [46, 47]. Regions of LPFC included Fp1 and F7 with the readings from channels 1-4 averaged. Regions of RPFC included Fp2 and F7 with readings from channels 5-8 averaged. The measurement location was replicated between trials by locating the nasion site (distinctly depressed area directly between the eyes, just superior to the bridge of the nose) and placing the edge of the headband 2 cm above this point (1 cm above the eyebrows), and the middle of the headband in the center of the forehead [48]. In order to reduce possible artifact (movement and heart rate) a band-pass filter of 0.01 to 0.50 Hz was applied to the fNIRS signal [49]. Once the cap was positioned properly, participants had 2 min of seated rest with minimal movement to allow them to achieve a rested state. The Trail-Making Test (TMT) Part B was used as a within-condition control prior to the NIH Toolbox test. The TMT Part B has been shown to increase PFC oxygenation [50]. Relative concentration changes for O$_2$Hb and HHb were measured from resting baseline within each trial (pre and post) using the first 10 seconds following the 2-min resting period, and defined as 0 mol. The fNIRS device is capable of quantifying PFC oxygenation and total blood flow [51]. The most sensitive measure of cerebral oxygenation is the oxyhemoglobin difference (Hbdiff) due to the high correlation with CBF and mean arterial pressure.
(MAP) changes [51-53]; tHb best reflects the changes in regional blood volume [54, 55]. Hbdiff has a linear relationship with MAP, CBF, and flow velocities; and, has been used as a marker of cerebral hemorrhage, and hypotension in critically ill patients [53]. During the cognitive tasks and submaximal treadmill walk test, the Hbdiff and tHb were used to evaluate PFC oxygenation and changes in PFC blood volume, respectively [56]. Data were recorded at a signal sampling of 10 Hz and averaged for each variable across both RPFC and LPFC to provide an index of regional PFC oxygenation. A differential pathlength factor (DPF) of 4.94 was used and adjusted according to the participants age, in accordance with the findings of Duncan et al. [57]. The DPF corrects the measured optode separation distance for light scattering within the sample [51]. Figure 2 shows the placement of the optodes on the participant’s forehead.

[insert Figure 2.]

### 2.5 Cognitive Function

Cognition was evaluated before and after 18 sessions of CR using the NIH Toolbox Cognition Battery, specifically the Fluid Cognition test battery. The fluid cognition battery for ages 3-85 years was delivered using an iPad device. The test battery consisted of five separate tests to assess cognition and included: 1. Pattern comparison test measuring processing speed; 2. Picture sequence memory test measuring episodic memory; 3. Flanker inhibitory control and attention test measuring executive function and attention; 4. Dimensional change card sort test measuring executive function; and 5. List sorting working memory test measuring working memory. The fluid cognition battery was chosen because it is considered a more global assessment of the ability to
solve problems, think, and develop autobiographical memories [58]. In addition to the scores for each separate cognitive test as mentioned above, the fluid cognition battery also provides a composite score which allows for general evaluation of overall cognitive functioning [58]. Fluid abilities appear to be more responsive to changes in brain functioning as a result of an intervention (e.g., chronic exercise), aging, or disease state [58]. Fully corrected T-scores (mean (SD) score was 50 (10)) were generated for each cognitive test and for the overall composite score. This approach is recommended by the developers as it compares the participant with a nationally representative sample from the NIH toolbox while adjusting for key demographic variables such as age, gender, race/ethnicity, and educational attainment [58]. A score of 50 indicates performance at the national average for the demographic information of that participant. The NIH Toolbox assessment for fluid cognition has been validated and deemed reliable among healthy adults ages 20-85, suggesting it can be used effectively in epidemiologic and clinical studies [59]. Total test administration requires approximately 20-25 min. Participants wore the fNIRS headband during the entire cognitive assessment session to prevent any measurement site differences between tests.

2.6 Cardiovascular Evaluation

Functional exercise capacity was estimated by metabolic equivalent of task (METs) as derived from a standardized, symptom-limited submaximal graded treadmill (TM) stress test (Quinton Cardiology, Deerfield, Wisconsin). This test was performed before and after 18 CR sessions. Specifically, the exercise test began with a 30-second warm-up at 1 mph and 0% incline with an alternating increase in stage speed (mph) or
incline (%) every 60 seconds with speed changing first. The test was terminated at an
RPE of 5 on the 0-10 scale [45]; at the patient’s request; or due to evidence of
cardiovascular, neurologic, or musculoskeletal decompensation. Exercise capacity was
estimated in METs at the TM test endpoint [60].

2.7 Statistical Analysis

Sample size was determined based on a priori calculation with power set to 0.80
and alpha level of 0.05 (G*power, Dusseldorf, Germany). The criterion for selected
studies was a long-term exercise intervention and changes in global cognitive function
[61, 62]. The estimated effect size was 0.8, which estimated a minimum of seventeen
patients to detect a difference using the analyses selected. All results are expressed as
means (SD) and evaluated for homogeneity of variance and normality. All PFC responses
(Hbdiff, tHb, O₂Hb, and HHb) were analysed from the RPFC and LPFC regions. Data
from the leftmost region (fNIRS channels 1-4) rightmost region (fNIRS channels 5-8)
were used to represent the LPFC and RPFC, respectively [63]. Student’s t-tests were used
to compare pre and post changes in NIH Toolbox cognitive test scores and all PFC
responses for both LPFC and RPFC. Student’s t-tests were also used changes between
regional PFC responses (LPFC vs. RPFC). Bivariate Pearson correlational analyses were
used to evaluate the relationship between the change in NIH Toolbox test scores, change
in pre- and post-functional capacity and change in PFC activation during cognitive testing
via fNIRS (both LPFC and RPFC). Effect size was established using Cohen’s d, where
0.2, 0.5, and 0.8 represent a small, medium, and large effects, respectively [64]. Data
were analyses using IBM SPSS Statistics (version 25.0, Chicago, IL).
RESULTS

3.1 Participant Characteristics and Changes in Cardiovascular Fitness

Participant height, weight, estimated peak oxygen consumption (VO$_{2peak}$), and submaximal walking test time are shown in table 1. No significant differences in weight or BMI were noted between pre- and post-CR timepoints. After the CR intervention, estimated peak functional capacity increased by 1.4 METs and average TM walk time increased by 1.5 min ($p < 0.01$). Participants completed an average (SD) of 19.7 (1.5) CR sessions over an average (SD) of 65 (16) days.

3.2 Change in Cognitive Performance

Cognitive scores post-CR showed a significant improvement in four (processing speed, attention, executive function, and working memory) of the five cognitive tests measured by the NIH toolbox (Table 2). No significant difference was found in episodic memory scores ($p > 0.05$). Overall cognitive functioning (fluid composite score) also improved significantly ($p < 0.01$).

[insert Table 2.]

3.3. Change in PFC Oxygenation during Cognitive Testing

Regions of interest were the LPFC and RPFC; PFC responses of interest were Hbdiff, tHb, O$_2$Hb, and HHb (Table 3, Figures 3-7). A significant improvement was seen in the RPFC in the Hbdiff response for both the executive function and working memory tests ($p < 0.05$). In the LPFC, Hbdiff increased across all five cognitive tests ($p < 0.05$). LPFC O$_2$Hb increased across four cognitive tests (processing speed, episodic memory, attention, and executive function ($p < 0.05$), and LPFC tHb increased in three cognitive
tests (processing speed, episodic memory, and attention) ($p < 0.05$). No significant regional differences (LPFC vs. RPFC) were detected for the cognitive tests.

3.4 Cognition, Cardiovascular Fitness and PFC Oxygenation

Results of bivariate Pearson correlational analyses between the change in cognitive scores and change in regional PFC measures pre- and post-CR are shown in Table 4. Significant negative associations were found in RPFC and LPFC Hbdiff for the fluid composite score (RPFC Hbdiff: $r = -0.467$, $p = 0.038$; Figure 8A; LPFC Hbdiff: $r = -0.447$, $p = .048$, Figure 8D), and in the LPFC $O_2$Hb and tHb during the dimensional test (LPFC $O_2$Hb: $r = -0.445$, $p = 0.049$, Figure 8B; LPFC tHb: $r = -0.487$, $p = .030$, Figure 8C). Bivariate Pearson correlational analyses were also used to evaluate the relationship between the change in cardiovascular fitness ($\text{MET}_{\text{peak}}$) and changes in cognitive scores and PFC measurements pre- and post-CR. There were no significant differences between changes in PFC measurements and change in cardiovascular fitness. However, the change in cardiovascular fitness was positively associated with working memory score ($r = 0.546$, $p = 0.016$), but no other cognitive test score (Figure 9).

 DISCUSSION

The main findings of the current study were that CVD patients showed improvements in global cognition and changes in PFC oxygenation patterns during cognitive testing following 6 weeks of a CR program. Specifically, participants had
improvements in post-CR processing speed, attention, executive function, and working memory scores in addition to increased PFC oxygenation during post testing. Correlational analyses also indicated negative associations between PFC oxygenation and cognitive tests (executive function and fluid composite scores) which may indicate improvements in neural efficiency as represented by lower oxygen demand for cognition-related tasks in a specific PFC region.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM5) [65], mild neurocognitive disorder may be defined as cognitive performance in at least one cognitive domain that is one or more SD below average using age- and education-adjusted normative data. In utilizing such guidelines, 12 participants met this definition for mild neurocognitive impairment (60% of sample) pre-CR; this was decreased to 3 participants (15% of sample) post-CR. Therefore, our findings suggest that CVD patients, similar to those in our sample, displaying mild neurocognitive disorder may have substantial improvements after 6 weeks of CR. Our current results support findings reported in previous research. Specific to CVD patients, Gunstad et al. [15] found that 12 weeks of CR improved visual attention and psychomotor speed in addition to visual speeded search and scanning abilities. In addition, Stanek and colleagues [16] reported improved global cognition, attention-executive-psychomotor function, and memory after 12 weeks of CR. Specific to the study by Stanek et al. [16], verbal memory performance scores increased by nearly 20% after 12 weeks of CR which was similar to the current results for working memory (increased by 11%) given this intervention was approximately 6 weeks or half the duration. CR was also shown to improve attention/executive function performance in heart failure patients [66].
populations who display cognitive impairments, evidence also supports the aforementioned findings. For example, Quane et al. [67] found that 8 weeks of aerobic exercise (3 times per week) improved information processing speed in stroke survivors, while a 16-week aerobic exercise intervention was found to be equally effective as antidepressants in reducing depression among patients with major depressive disorder [68]. The current findings are in line with previous research and overwhelmingly in favor of CR as a method of improving cognitive function in CVD patients. It is our belief that CR interventions have benefit as an adjunctive therapy for other cognitively impaired populations; replication of this current study using more heterogeneous samples is recommended.

In the present study PFC activation increased during cognitive testing following CR. The oxyhemoglobin and hemoglobin difference represent the relative concentrations of arterial oxygen content and oxygen extraction, respectively, within the PFC region monitored by the fNIRS device. The PFC is thought to govern cognitive processes such as information processing, attention, and working memory [29]. Recently, several neuroimaging studies have investigated relationships between acute aerobic exercise and PFC oxygenation during a cognitive task post-exercise; however, chronic exercise studies exploring the pre- and post-intervention changes in PFC responses and cognition in clinical populations are scarce [63, 69, 70]. Nevertheless, chronic exercise studies that have investigated these parameters have yielded mixed results. For example, a 16-week moderate-intensity exercise intervention in older adults showed significant decreases in tHb and increases in HHb in the LPFC during naming and executive function tasks [26]. Conversely, Xu et al. [71] found that overweight/obese individuals who underwent a 4-
A 7-week fitness intervention had higher O$_2$Hb of the left ventrolateral and bilateral dorsolateral PFC due to the Stroop effect (a measure of executive function) and lost more weight than those participants with lower activation of these neural regions. Similar to the aforementioned result, Chen et al. [72] report 8 weeks of mind-body training (5 days/week, 90 min/day) improved Flanker scores and increased O$_2$Hb in the LPFC in healthy college students. The current findings show increased PFC activation across multiple variables of interest for all five cognitive tests following CR. Specifically, it appears the LPFC plays a larger role in changes following a chronic exercise intervention. Increased activation in the LPFC as opposed to the RPFC is logical as the LPFC region houses the left-dorsolateral area (DLPFC) which is considered the main site within the PFC for manipulating verbal and spatial knowledge in working memory [73]. This region has been shown to be highly active during dual task conditions in which two simultaneous tasks had to be coordinated, similar to the demands of the cognitive tests in the current study [74]. The increase in PFC activation during cognitive testing found in the present study differs from the decreased activation (decreases in tHb and increases in HHb) results outlined above [26] and may be due to the shorter duration aerobic exercise intervention or the more comprehensive cognitive assessment in the current investigation. Overall, these data add to the literature by demonstrating that a chronic aerobic exercise intervention in CVD patients enhances post-CR PFC oxygenation during various cognitive tests.

The associations between the change in several cognitive test scores and PFC responses reveal a variety of negative correlations. These findings demonstrate that, for our sample, an increase in PFC oxygenation occurred but was not linked to improvements
in cognitive function. In fact, we observed a negative relationship between various
cognitive constructs and PFC oxygenation; this may indicate improved neural efficiency
[75]. More specifically, less PFC input (measured through oxygenation) was required for
a given output (measured by cognitive performance testing). Similar observations have
been made among older adults in response to physical activity interventions. For
example, Nishiguchi et al. [61] report that decreased brain activation was associated with
short-term memory improvements in the PFC following a 12-week exercise intervention
in community-dwelling older adults. In addition, Smith et al. [77] found that a 12-week
moderate-intensity treadmill walking intervention decreased brain activation during a
semantic memory task in both mild cognitively impaired and cognitively intact older
adults. Previous results combined with the current demonstrate a possible improvement in
neural processing as a result of participation in aerobic exercise training, such as cardiac
rehabilitation. Therefore, PFC activation may not mediate the improvements in cognitive
function, but may help to identify the adaptation to exercise.

Given the findings in the present study, future research among CVD patients is
warranted in order to locate the specific mechanisms by which CR benefits cognitive
function. Findings from the current study indicate that changes in functional capacity and
PFC oxygenation responses during cognitive testing do not account for the improvements
in cognitive testing scores. Increased aerobic fitness has been shown to be associated with
better cognitive function in young and old healthy individuals in addition to those with
CVD [15, 77-79]; however, in the current study, increased aerobic capacity was only
positively associated with working memory, and no other cognitive test. Similarly,
increased cerebral oxygenation and blood flow responses during cognitive testing have
been shown to be related to improved cognitive function in older adults and those with hypertension [79, 80]. In the current study, changes in both LPFC and RPFC regions were inversely associated with certain cognitive parameters, which may represent increased neural efficiency and an adaptation to the exercise intervention. Future research is needed to explain and elaborate upon the neurophysiological mechanisms of cognitive-related benefits following CR. Recent research by Saleem et al. [81] found that a lower reactive hyperemia index (RHI), a measure of endothelial dysfunction, was associated with poorer verbal memory in CAD patients at baseline; additionally, an increased RHI over 3 months was related to an improved processing speed score. This may indicate that monitoring endothelial dysfunction may be a clinically useful predictor of cognitive function in patients with CAD and that benefits in vascular function may play a major role in cognitive changes before and after CR. Similarly, it has been increasingly acknowledged that dysregulated lipid pathways have been associated with neurocognitive diseases (such as Alzheimer’s and Parkinson’s disease) [82-84], suggesting that there may be a link between changes in lipid profiles and cognitive dysfunction in CVD patients. Sphingolipids have been highlighted as a lipid that may be linked to cognitive dysfunction; specifically, a decrease in sphingolipid - ceramide C18 has been significantly associated with improvements in multiple cognitive domains (verbal memory, visuospatial memory, processing speed and global cognition) in CAD patients after 6 months of CR [85]. In this light, perhaps changes in blood lipids also have an important role to play in changes in cognition following CR in CAD patients. As a result of this, it should be mentioned that perhaps dietary changes, statin or other medication use, or exercise performed outside of CR may have had a confounding influence on the
results (although no covariance analysis was performed) and should be accounted for in future research that involves exercise interventions and cognitive changes. Further research may also be able to model these mechanisms and specify which ones are heavily involved in cognitive improvements following an exercise intervention.

The current study has certain limitations that should be addressed. First, the small sample size and recruitment from a single CR center may produce potential recruitment bias. Participants in this group were also receiving thorough medical therapy (e.g., medication and education) and following a supervised aerobic exercise program; this may have influenced cognitive results. Results from the current study may differ in other cardiac patients (e.g., acute coronary syndromes) in the real-world setting for those who do not have access to similar medical and individualized exercise therapies. In addition, PFC oxygenation and blood flow were assessed using fNIRS technology for the left and right PFC areas indicating a limited cortical region and a relatively superficial brain tissue measurement (light penetration approximately 2.25 cm). Therefore, our results may differ from those of studies using more global and invasive measures of cerebral oxygenation and blood flow (e.g., catheters) or including other brain regions which may provide additional insight into the post CR responses in CVD patients during cognitive testing.

In summary, results from the current investigation suggest that cognitive dysfunction and PFC oxygenation in CVD patients are modifiable after 6 weeks of CR. In addition, patients displayed an improvement in neural efficiency which may represent an adaptation to the exercise intervention. These outcomes provide clinicians and exercise specialists alike with significant practical implications. While cognitive
dysfunction remains high in CVD patients, it is possible to improve cognitive function and PFC blood flow responses via an aerobic exercise intervention. Future research should focus on identifying the exact physiological mechanisms responsible for the improvements that mediate these changes while also taking into account outside influences (e.g., dietary changes, medications and exercise performed outside of CR). The present study also highlights the potential use of fNIRS technology to provide non-invasive data to assess PFC responses during cognitive tasks in clinical settings. Increasing cognitive function and PFC activation may have the profound ability to lessen the rate of neurocognitive impairment and improve the quality of life in individuals with CVD. Taken together, individualized aerobic exercise interventions (i.e., CR) provide significant cognitive benefits. In addition, the present study has benefit for the cardiologists as it illustrates the additional benefits of referring qualifying patients to CR programs. Given these significant findings, perhaps cognitive measurements at the beginning and upon completion of a CR program should also become a standard practice for these patients.

**Clinical Message**

- Exercise-based cardiac rehabilitation increases PFC oxygenation and improves cognitive performance; however, this does not appear to be responsible for the improvement in cognitive performance.

- An adaption to the exercise intervention may be an improvement in neural efficiency.

- Cardiac rehabilitation produces benefits beyond one’s aerobic capacity.
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Declaration of conflicting interests

The authors declare that there is no potential conflict of interest.

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References


58. NIH. NIH Toolbox scoring and interpretation guide, October 2016.


Table 1. Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Anthropometric characteristics</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender n (M/F)</td>
<td>20 (15/5)</td>
<td>-</td>
</tr>
<tr>
<td>Age yrs</td>
<td>64.8 (11.6)</td>
<td>-</td>
</tr>
<tr>
<td>Height cm</td>
<td>170.8 (11.2)</td>
<td>-</td>
</tr>
<tr>
<td>Weight kg</td>
<td>86.1 (19.6)</td>
<td>85.6 (19.4)</td>
</tr>
<tr>
<td>Body mass index kg/m²</td>
<td>29.4 (5.9)</td>
<td>29.2 (5.8)</td>
</tr>
<tr>
<td>Functional Capacity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>METs</td>
<td>5.5 (2.5)</td>
<td>6.9 (2.8)**</td>
</tr>
<tr>
<td>Walking time min</td>
<td>6.3 (3.1)</td>
<td>7.8 (3.5)**</td>
</tr>
</tbody>
</table>

| Etiology                      |              |              |
| Coronary Artery Disease n (%) | 17 (85%)     | -            |
| Diabetes Mellitus (Type 1 or 2) n (%) | 5 (25%) | -            |
| Congestive Heart Failure n (%) | 3 (15%)      | -            |

| Medications                   |              |              |
| β-Blocker n (%)               | 18 (90%)     | -            |
| ACE inhibitor/ARB n (%)       | 11 (55%)     | -            |
| Ca²⁺ channel blocker n (%)   | 2 (10%)      | -            |
| Diuretic n (%)                | 5 (25%)      | -            |
| Statin n (%)                  | 18 (90%)     | -            |

**p = <0.01, pre vs. post**

Data are mean (SD), yrs = years, cm = centimeters, kg = kilogram, kg/m² = kilogram/square meter, min = minutes, METs = Metabolic Equivalents, ACE = Angiotensin converting enzyme, ARB = Angiotensin receptor blocker, Ca²⁺ = calcium. N=20.
Table 2. Results from the NIH Toolbox fluid cognition test before and after 18 sessions of cardiac rehabilitation. N = 20.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Cohen’s d (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive test (construct)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pattern comparison (processing speed)</td>
<td>46 (15)</td>
<td>58 (11) **</td>
<td>1.35 (7.7-15.8)</td>
</tr>
<tr>
<td>Picture sequence (episodic memory)</td>
<td>47 (10)</td>
<td>51 (8)</td>
<td>.43 (-.30-.77)</td>
</tr>
<tr>
<td>Flanker (attention)</td>
<td>42 (9)</td>
<td>51 (7) **</td>
<td>0.79 (3.4-13.4)</td>
</tr>
<tr>
<td>Card sort (executive function)</td>
<td>54 (8)</td>
<td>60 (10) **</td>
<td>.85 (2.8-9.9)</td>
</tr>
<tr>
<td>Work memory (working memory)</td>
<td>48 (6)</td>
<td>54 (7) **</td>
<td>.98 (3.2-9.2)</td>
</tr>
<tr>
<td>Cognitive fluid composite (global abilities)</td>
<td>46 (8)</td>
<td>57 (9) **</td>
<td>2.04 (8.3-13.1)</td>
</tr>
</tbody>
</table>

**p = <0.01, pre vs. post
Data are mean (SD) and Cohen’s d effect size (95% CI), CI = Confidence interval.
Table 3. Pre- and post-cardiac rehabilitation summary table for change in left and right prefrontal cortex (LPFC and RPFC) oxyhemoglobin (O$_2$Hb), deoxyhemoglobin (HHb), total hemoglobin (tHb), and hemoglobin difference (Hbdiff) responses during cognitive testing. N = 20.

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>RPFC O$_2$Hb (μmol)</th>
<th>LPFC O$_2$Hb (μmol)</th>
<th>Cohen’s $d$ (95% CI)</th>
<th>RPFC HHb (μmol)</th>
<th>LPFC HHb (μmol)</th>
<th>Cohen’s $d$ (95% CI)</th>
<th>RPFC tHb (μmol)</th>
<th>LPFC tHb (μmol)</th>
<th>Cohen’s $d$ (95% CI)</th>
<th>RPFC Hbdiff (μmol)</th>
<th>LPFC Hbdiff (μmol)</th>
<th>Cohen’s $d$ (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Pre Mean (SD)</td>
<td>Post Mean (SD)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td>.98 (1.14)</td>
<td>1.19 (1.12)</td>
<td>.16 (.52-.97)</td>
<td>.94 (1.23)</td>
<td>1.36 (1.27)**</td>
<td>.40 (.19-.70)</td>
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<tr>
<td>Episodic memory</td>
<td>2.07 (1.41)</td>
<td>2.24 (1.35)</td>
<td>.09 (-.24-.53)</td>
<td>1.99 (1.43)</td>
<td>2.46 (1.47)**</td>
<td>.34 (.17-.85)</td>
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<tr>
<td>Attention</td>
<td>1.97 (1.67)</td>
<td>2.33 (1.55)</td>
<td>.17 (-.14-.84)</td>
<td>1.73 (1.92)</td>
<td>2.51 (1.74)**</td>
<td>.37 (.30-1.30)</td>
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<tr>
<td>Executive function</td>
<td>2.06 (1.73)</td>
<td>2.50 (1.56)</td>
<td>.20 (.08-.94)</td>
<td>1.95 (2.12)</td>
<td>2.66 (1.92)*</td>
<td>.30 (.17-.23)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Working memory</td>
<td>2.32 (2.33)</td>
<td>2.77 (1.76)</td>
<td>.16 (-.17-.93)</td>
<td>2.77 (1.76)</td>
<td>2.80 (2.19)</td>
<td>.18 (-.14-1.16)</td>
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RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, $O_2$Hb = oxyhemoglobin, HHb = deoxyhemoglobin, $t$Hb = total hemoglobin, Hbdiff = oxyhemoglobin difference, CI = confidence interval, $\mu$mol = micromole. Data are mean (SD) and Cohen’s $d$ effect size (95% CI), $^*p = <0.05$, $^{**}p = <0.01$. 
Table 4. Correlational analyses summary table for change in left and right prefrontal cortex (LPFC and RPFC) responses and change in cognitive test scores. N = 20.

<table>
<thead>
<tr>
<th></th>
<th>RPFC</th>
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RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, O$_2$Hb = oxyhemoglobin, HHb = deoxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. Data are $r$-value ($p$-value). *$p = <0.05$. 
Figure 1. Outline of the study protocol. Number of Cardiac Rehabilitation (CR) sessions are mean (SD).
Figure 2. Schematic representation of functional near-infrared spectroscopy (fNIRS) optodes. Open circles with numbers (1-8) represent light sources (optodes or transmitters), and open circles with R1 and R2 represent receivers. Eight channels were created with 1-4 monitoring the LPFC and 5-8 monitoring the RPFC. LPFC = left prefrontal cortex. RPFC = right prefrontal cortex.
Figure 3. Prefrontal cortex responses during the processing speed task pre and post CR. A significant difference in LPFC $O_2$Hb (A) was observed pre and post CR. No significant differences were observed in RPFC or LPFC HHb (B). Significant differences were also observed in LPFC tHb (C) and LPFC Hbdiff (D) pre and post CR. CR = cardiac rehabilitation, RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, $O_2$Hb = oxyhemoglobin, HHb = deoxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. N=20.
Figure 4. Prefrontal cortex responses during the episodic memory task pre and post CR. A significant difference in LPFC $O_2$Hb (A) was observed pre and post CR. No significant difference was observed in RPFC or LPFC HHb (B). Significant differences were observed in LPFC tHb (C) and LPFC Hbdiff (D) pre and post CR. CR = cardiac rehabilitation, RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, $O_2$Hb = oxyhemoglobin, HHb = deoxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. N=20.
Figure 5. Prefrontal cortex responses during the attention (flanker) task pre and post CR. A significant difference in RPFC and LPFC O₂Hb (A) was observed pre and post CR. No significant differences were observed in RPFC or LPFC HHb (B). Significant differences were also observed in LPFC tHb (C) and LPFC Hbdiff (D) pre and post CR. CR = cardiac rehabilitation, RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, O₂Hb = oxyhemoglobin, HHb = deoxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. N=20.
Figure 6. Prefrontal cortex responses during the executive function task pre and post CR. A significant difference in LPFC $O_2$Hb (A) was observed pre and post CR. No significant differences were observed in RPFC or LPFC HHb (B) or tHb (C). Significant differences were also observed in RPFC and LPFC Hbdiff (D) pre and post CR. CR = cardiac rehabilitation, RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, $O_2$Hb = oxyhemoglobin, HHb = deoxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. N=20.
Figure 7. Prefrontal cortex responses during the working memory task pre and post CR. No significant differences were observed in RPFC or LPFC O₂Hb (A), HHb (B) or tHB (C) from pre to post CR. A significant increase in RPFC and LPFC Hbdiff (D) were observed. CR = cardiac rehabilitation, RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, O₂Hb = oxyhemoglobin, HHb = deoxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. N=20.
Figure 8. Relationships between the changes in prefrontal cortex responses and changes in cognitive test scores. Significant negative relationships were detected between the changes in: RPFC Hbdiff and composite score change (A), LPFC O$_2$Hb and executive function change (B), LPFC tHb and executive function change (C), LPFC tHb and composite score change (D). RPFC = right prefrontal cortex, LPFC = left prefrontal cortex, O$_2$Hb = oxyhemoglobin, tHb = total hemoglobin, Hbdiff = oxyhemoglobin difference. N=20.
Figure 9. Relationship between change in cardiovascular fitness and change in working memory score. A significant positive relationship was detected between the change in cardiovascular fitness (METs) and change in working memory score. METs = metabolic equivalents. N=20.
CHAPTER 4: SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

Summary

The novelty of this study was that it was the first to examine and compare the cognitive changes and prefrontal cortex (PFC) oxygenation responses to 6 weeks of cardiac rehabilitation (CR) in cardiovascular disease (CVD) patients. Specifically, we investigated if CR exercise training would improve cognitive performance and if these changes were associated with increased PFC oxygenation during such cognitive tasks in patients with CVD. The research manuscript entitled, “Cardiac Rehabilitation Increases Cortical Activation During Cognitive Testing” found in Chapter 3 provides evidence that 6 weeks of CR has the ability to lessen, and possibly reverse the mild cognitive impairments found in patients with CVD. Furthermore, this type of aerobic exercise intervention has the ability to increase cortical hemodynamics and improve neural efficiency. In conclusion, CR can have a profound cognitive impact in individuals with CVD, ultimately improving their quality of life.

Conclusions

The utilization of and adherence to CR has the ability to improve cognitive function in patients with CVD as in those who were recruited for the current study. Specifically, as few as 19 sessions of CR could increase cognitive test scores and improve PFC oxygenation. In addition, patients displayed an increased neural efficiency which may represent an adaptation to the exercise intervention. It is also interesting to note that despite the nonsignificant difference in post-CR episodic memory score, this result may be clinically significant given the medium effect size. These findings further
highlight the importance of administering individualized aerobic exercise sessions for patients in this population. We conclude the following regarding our study of cognitive performance and PFC hemodynamics during cognitive testing in CVD patients:

- Engaging in CR can improve cardiovascular fitness and multiple cognitive domains.
- Measurements of PFC oxygenation during cognitive testing are increased following 6 weeks of CR; however, this does not appear to be responsible for the improvement in cognitive performance.
- Increased neural efficiency may represent an adaptation to CR in CVD patients.

**Recommendations**

These findings have prompted consideration for the following future investigations:

1. Investigating the effect of CR for other homogenous samples (age, sex, specific type of CVD).
2. Investigating the cognitive and PFC response to prerehabilitation (engaging in an aerobic exercise intervention prior to cardiac surgery).
3. Exploring the long-term cognitive and PFC changes following completion of a CR program, and making follow-up measurements at more distal time points (e.g., 3, 6, 9, 12 months after CR is completed).
4. Examining the relationship between the intensity of aerobic exercise performed during CR and cognitive performance may have some unique practical programming applications.
5. Exploring other physiological markers may be noteworthy in trying to determine the exact mechanisms responsible for cognitive changes.

6. Investigating other areas of the brain may provide us with additional insight into the changes in activity patterns following CR.
APPENDICES

A. Informed Consent

B. Data Collection Sheets

C. Atterbom Submaximal Exercise Test Protocol
APPENDIX A.

The effects of cardiac rehabilitation on cognitive function and hemodynamics

Consent to Participate in Research
1/23/19

Purpose of the research: You are being asked to participate in a research study that is being done by Micah Zuhl, the Principal Investigator, and his associates from the department of Health, Exercise, and Sports Sciences at the University of New Mexico. The purpose of this study is to examine how an exercise program influences brain function among those attending the New Heart cardiac rehabilitation exercise program. You are being asked to take part in this study because you are an English-speaking individual, enrolled in a Cardiac Rehabilitation program at New Heart Clinic, Albuquerque and live in Bernalillo County. A total of fifty subjects will be recruited for this study.

This form will explain what to expect when joining the research study. The possible risks and benefits of participation will be explained. If you have any questions, please ask one of the study researchers.

Key information for you to consider:
- You are being asked to participate in pre and post cardiac rehabilitation testing to examine how exercise influences brain function. This testing involves wearing a head cap while completing certain cognitive tasks. You will also wear this head cap during exercise, which is part of New Heart pre and post testing procedures. You are being asked to take part in this study because you are an English-speaking individual, enrolled in a Cardiac Rehabilitation program at New Heart Clinic, Albuquerque and live in Bernalillo County.
- Major requirements of the research: Measurements of brain blood flow during cognitive testing and exercise. There is also an OPTIONAL blood draw.
- The most important risks include: temporary pain or discomfort from blood draw (OPTIONAL), some frustration completing the concentration tasks, irritation from the brain cap or possible loss of privacy and confidentiality associated with participating in a research study.
- The most important benefit includes: identifying how cardiac rehabilitation exercise programs may improve cognitive function and brain oxygenation in cardiac patients.

The time to collect the measurements will be one hour, and total time to complete the study will be an estimated two hours (1 hour at pre-rehab and 1 hour at post-rehab).

What you will do in the project: Your participation will involve two measurement sessions that will take place at your baseline testing (pre-rehab) and after completion (post-rehab) of your cardiac rehabilitation program. All measurements will take place at
the New Heart clinic. These two visits will be scheduled by employees at the New Heart facility. The details of the visits are presented below.

1. Measurement of brain blood flow during cognitive testing. You will be fitted with a head cap that will cover the front of your head. This cap will be connected to several wires. You will sit quietly for 1 minute while the activity in your brain is measured using light waves. This is painless and only measures the amount of oxygen your brain is using. This measurement is called a functional near-infrared spectroscopy (fNIRS). You will then complete a 25-minute cognitive test while your brain activity is recorded by the fNIRS. The cognitive testing will be administered on a tablet computer.

2. Measurement of brain blood flow during exercise. The cap from step 2 will remain on your head, and your brain activity will be measured while you exercise. The exercise test is part of the pre and post testing at New Heart.

**OPTIONAL:** A blood sample will be collected from a vein in one of your arms to measure a protein called brain derived neurotrophic factor. A total of 7mL (0.50 tbsp) will be collected at both pre and post rehabilitation. The blood collection is not required and you are able to decline this procedure.

**OPTIONAL:** Blood samples will be collected using a needle stick technique. The blood draw will involve cleaning the puncture site with 70% alcohol solution. A straight needle or sterile smaller needle with plastic stabilizers (butterfly needle) will be used to draw blood into plastic blood collection tubes. Immediately following the blood draw, the puncture site will be covered with a band-aid. All equipment used in the process will be placed in specific containers for throwing away. The blood draw work area (i.e., work bench, or examination table) is then wiped down using a 70% alcohol solution using paper towel. You will be monitored after each blood draw. If you have a fear of needles or feel uncomfortable, you will be able to lay down prior to and after the blood draw. Two total blood draws will take place during the study, one at pre, and one at the end of the Cardiac Rehabilitation program.

In addition to the above measurements, we will also document your results from each exercise session you attend at New Heart. This will include how much exercise you perform and the intensity of the exercise. We will also document your results on all of your pre-rehab and post-rehab tests. This will include all questionnaires and exercise testing results.

The time to collect the measurements will be one hour, and total time to complete the study will be an estimated two hours (1 hour at pre-rehab and 1 hour at post-rehab).

**Risks:** Blood collection (OPTIONAL). Collecting your blood may cause temporary pain and discomfort from the needle sticks and from the finger or earlobe pricks. There could be a possibility of bruising, sweating, feeling faint or lightheaded, and in rare cases there is risk of infection. To minimize risk, proper blood drawing techniques will be used, which will include technician wearing sterile (non-latex) protective gloves, thorough
cleaning of site, and sterile needles. The site will be covered after the blood draw to prevent infection. All members of the research team are trained by these standards.

Mental stress. You may have some frustration during the concentration tasks. These tasks are designed to challenge your memory and ability to recall facts in a certain amount of time. If you become upset during the concentration tasks then the test will be stopped.

Brain cap. You may have some redness or irritation on the forehead area from the cap itself. For example, some people report minor irritation at the electrode site.

There are risks of stress, emotional distress, inconvenience and possible loss of privacy and confidentiality associated with participating in a research study.

**Benefits:** There are no other direct benefits to you from participating in this study. However, it is hoped that information gained from this study will help us investigate and identify the mechanisms of how cardiac rehabilitation may improve cognitive function and brain oxygenation in cardiac patients.

**Confidentiality of your information:** To protect your information, you will receive a subject number with no link to your name on any study material. Only the research team will know what you do or say in this study. All health history information will be viewed only by the research team. The purpose of health information is to determine your eligibility for the study. Your information will be stored in a locked cabinet in Micah Zuhl’s office. While some members of the research team may be your teacher, your participation or non-participation will have no impact on your grade in class.

We will take measures to protect the security of all your personal information, but we cannot guarantee confidentiality of all study data. The University of New Mexico Institutional Review Board (IRB) that oversees human subject research and/or other entities (such as a Sponsor) may be permitted to access your records. The Food and Drug Administration (FDA) may also inspect your records. Your name will not be used in any published reports about this study.

You should understand that the researcher is not prevented from taking steps, including reporting to authorities, to prevent serious harm of yourself or others.

**Use of your information for future research:** Your information collected for this project will NOT be used or shared for future research, even if we remove the identifiable information like your name or date of birth.

**Payment:** In return for your time in this study, you will be paid a cash sum of for each visit, for a total of $60. If you do not complete the study, you will be paid $30 for each visit you completed. Compensation is considered taxable income. Amounts of $600 or more will be reported by UNM to the Internal Revenue Service (IRS).
**HIPAA Authorization for Use and Disclosure of Your Protected Health Information (HIPAA)**

As part of this study, we will be collecting health information about you and sharing it with others. This information is “protected” because it is identifiable or “linked” to you.

**Protected Health Information (PHI)**

By signing this Consent Document, you are allowing the following people to use your protected health information for the purposes of this study: Terence Moriarty, Micah Zuhl, Kelsey Bourbeau, Gabriella Bellissimo and Christine Mermier. This information may include: medical and physical activity history, cardiac condition, height, weight, age, exercise adherence, estimated maximal oxygen consumption, and heart rate.

In addition to researchers and staff at UNM and other groups listed in this form, there is a chance that your health information may be shared (re-disclosed) outside of the research study and no longer be protected by federal privacy laws. Examples of this include disclosures for law enforcement, judicial proceeding, health oversight activities and public health measures.

**Right to Withdraw Your Authorization**

Your authorization for the use and disclosure of your health information for this study shall not expire unless you cancel this authorization. Your health information will be used or disclosed as long as it is needed for this study. However, you may withdraw your authorization at any time provided you notify the UNM researchers in writing. To do this, please send a letter notifying them of your withdrawal to:

Micah Zuhl, Department of Health, Exercise, and Sports Sciences, Johnson Center B143 MSC04, 1 University of New Mexico, Albuquerque New Mexico 87131
Zuhl09@unm.edu.

Please be aware that the research team will not be required to destroy or retrieve any of your health information that has already been used or shared before your withdrawal is received.

If you have questions about the privacy practices of the entity from which your PHI is being collected, you can request a Notice of Privacy Practices from your provider.

**Refusal to Sign**

If you choose not to sign this consent form and authorization for the use and disclosure of your PHI, you will not be allowed to take part in the research study.
Right to withdraw from the research: Your participation in this study is completely voluntary. You have the right to choose not to join or to withdraw at any point with no penalty. If you decide to withdraw, your information will not be used in the study. Deciding to participate in this study (or not) will not affect the care that you receive at New Heart. If you experience any injury or are unable to complete both trials, then the research team will withdraw you from the study.

If you have any questions, concerns, or complaints about the research, please contact:

Micah Zuhl, Department of Health, Exercise, and Sports Sciences, Johnson Center B143 MSC04, 1 University of New Mexico, Albuquerque, NM 87131. (505) 277-3243. Zuhl09@unm.edu.

If you have questions regarding your rights as a research participant, or about what you should do in case of any harm to you, or if you want to obtain information or offer input, please contact the IRB. The IRB is a group of people from UNM and the community who provide independent oversight of safety and ethical issues related to research involving people:

UNM Office of the IRB, (505) 277-2644, irbmaincampus@unm.edu. Website: http://irb.unm.edu/

CONSENT

You are making a decision whether to participate in this research. Your signature below indicates that you have read this form (or the form was read to you) and that all questions have been answered to your satisfaction. By signing this consent form, you are not waiving any of your legal rights as a research participant. A copy of this consent form will be provided to you.

I agree to participate in this research.

Name of Adult Participant  Signature of Adult Participant  Date

I agree to the extra blood draw procedure  __________________________ initials

Researcher Signature (to be completed at time of informed consent)

I have explained the research to the participant and answered all of their questions. I believe that they understand the information described in this consent form and freely consents to participate.

Name of Research Team Member  Signature of Research Team Member  Date
APPENDIX B.

DATA COLLECTION SHEET
PRE

Subject#: ___________    Age: ___________    Time: ___________

Date: _______    Gender: ___________    Ethnicity: _______________

Ht (cm): ____    Wt (kg): ___    CVD type: ____________________

OPTIONAL: _______ 7ml venous blood collection (tube for serum – allow to clot for 20-
minutes. Spin at 2200 for 20 minutes (4°C))

Cognitive fNIRS Imaging

_______ fNIRS cap

_______ fNIRS while taking NIH Toolbox cognition tests

Save file as subject# and trial pre-cognition

Exercise fNIRS Imaging

_______ fNIRS cap

_______ fNIRS while performing the Atterbom exercise test

Save file as subject# and trial pre-exercise

_______ Treadmill estimated VO$_2$max (individual Atterbom protocol)

Speed = _____________ mph    Grade: ___________%

QoL score: ________________

Nutrition score: ________________

Depression score: ________________
DATA COLLECTION SHEET
POST

Subject#: ___________  Age: ___________  Time: ___________

Date: _______  Gender: ___________  Ethnicity: ___________

Ht (cm): ___  Wt (kg): ___  CVD type: ____________________

OPTIONAL: _______ 7ml venous blood collection (tube for serum – allow to clot for 20 minutes. Spin at 2200 for 20 minutes (4°C))

Cognitive fNIRS Imaging

_______ fNIRS cap

_______ fNIRS while taking NIH Toolbox cognition tests

Save file as subject# and trial pre-cognition

Exercise fNIRS Imaging

_______ fNIRS cap

_______ fNIRS while performing the Atterbom exercise test

Save file as subject# and trial pre-exercise

_______ Treadmill estimated VO\(_2\)\(_{\text{max}}\) (individual Atterbom protocol)

Speed = _____________ mph  Grade: ___________ = %

QoL score: _______________

Nutrition score: _______________

Depression score: _______________
### APPENDIX C.

Atterbom Submaximal Exercise Test Protocol

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min = minutes, mph = miles per hour, METs = Metabolic Equivalents.