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A RISK/BENEFIT ANALYSIS AND PRESCRIPTION OPTIMIZATION FOR INTEGRATING HIGH-INTESITY INTERVAL TRAINING INTO CARDIOPULMONARY REHABILITATION PROGRAMS

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By

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Abstract- A Risk/Benefit Analysis and Prescription Optimization for Integrating High-Intensity Interval Training into Cardiopulmonary Rehabilitation Programs

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Aerobic exercise is an effective solution for improving mortality rates and physical outcomes in patients with cardiovascular disease (CVD). There is a controversy, however, in the research literature over what type of training modality produces the best results. High-intensity interval training (HIIT) has emerged as a promising alternative to moderate-intensity continuous training (MCT), which is typically used to treat cardiovascular ailments. Currently, there is no consensus on the ideal HIIT prescription that would produce optimal benefits for patients, however. The goal of this review is to clarify whether HIIT provides either superior or equivalent outcomes in mortality, cardiac autonomic control, mitochondrial density, vascular homeostasis, cardiac structure, weight control, exercise adherence, and control other chronic diseases. In addition, this review analyzes the safety and programming considerations for including HIIT in cardiac rehabilitation facilities. Finally, an exercise prescription is presented, based on the literature, to suggest how HIIT prescriptions could be incorporated into traditional rehabilitation programs. After accounting for the potential benefits, risks, and integration considerations, this review recommends the use of HIIT in well-equipped rehabilitation programs after selecting interested, relatively fit, and low-risk patients.

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Introduction

Problem

Cardiovascular disease (CVD) is an insidious malady and a crucial public health issue, but it's an issue that our society can mitigate. Today, CVD is the leading cause of death in the United States with 600,000 deaths per year (Centers for Disease Control, 2017; Wilkins et al., 2017). The loss of life is further exacerbated by a tremendous financial burden to our healthcare system. Though difficult to quantify, in 2011 CVD accounted for at least 300 billion dollars in healthcare costs and lost productivity (Stinson,2015). Fortunately, the mortality rate has fallen in the U.S. since the 1980's primarily due to CVD risk factor management, like reductions in blood pressure and cholesterol, in addition to the use ameliorative options like stents, pacemakers, bypass grafts, and valve replacements (Institute of Medicine, 2010).

The trend of improving national CVD mortality, however, may stagnate without additional, widespread adoption of primary prevention techniques like diet and exercise. According to research by Wilmot, O'Flaherty, Capewell, Ford, and Vaccarino (2015), the reductions in CVD mortality could reverse in the U.S. as our population ages, the obesity epidemic worsens, and as people practice increasingly sedentary lifestyles. The research by Wilmot et al. further highlights how recent improvements in CVD mortality mainly occurred in older adults. Conversely, other vulnerable segments of our population such as people of low socioeconomic statues, ethnic minorities, and women have seen far less mortality improvement (Wilmot et al. 2015).

Widespread adoption of CVD risk factor modification via diet, exercise, mindfulness, and smoking cessation presents an attractive and cost-effective option that would galvanize further decreases in CVD mortality. These lifestyle modifications are effective at both preventing and mitigating new instances of CVD and can supplement recuperation in patients with existing CVD

(Dalal, Doherty, and Taylor). These modifications are currently used to promote CVD patient recovery during cardiac rehabilitation. Cardiopulmonary rehabilitation is an outpatient medical service that provides CVD and pulmonary patients with education, smoking cessation tools, psychosocial evaluation and support, in a setting where they can engage in medically supervised exercise.

A review by Gayda, Ribeiro, Juneau, and Nigam (2016) analyzes the different exercise forms traditionally used in cardiac rehabilitation, with moderate-intensity continuous training (MCT) currently the most frequently prescribed form of aerobic exercise. According to the review, MCT remains ubiquitous in cardiac rehabilitation prescriptions because of its proven safety and effectiveness at lowering mortality, morbidity, and cardiovascular symptoms and risk factors. Defining features of MCT training include: a short warm up and cool down, a static moderate intensity with few or no interruptions, typically between 50-75% of max heart rate, which is maintained for at least 10 minutes (Gayda et al, 2016). However, another type of exercise termed high-intensity interval training (HIIT) is generating excitement in cardiac rehabilitation research. The enthusiasm around HIIT stems from the protocol's ability to provide equivalent or superior physiological benefits as MCT. HIIT aims for a higher intensity, such as 85-100% of heart rate max, and alternates between intervals of high intensity and recovery intervals at a significantly lower intensity or with passive rest (Gayda et al, 2016).

A study by Keteyian et al. (2014) from the Henry Ford Health System demonstrated one superior physiologic benefits HIIT provides patients beyond MCT in a cardiac rehabilitation setting. The Keteyian et al. (2014) study randomized rehabilitation patients with various forms of stable CVD to either a HIIT or MCT group for ten weeks. The researchers investigated differences between the study groups by recording by evaluating resting and submaximal exercise heart rates,

changes in body mass, and the maximum ability to utilize oxygen (VO_2 peak) before and after a training protocol. Following the experimental period, the researchers found no differences in most of the variables measured, but participants in the HIIT group had improved VO_2 peak over the MCT group. The results of this study are noteworthy because VO_2 peak is tied to survival in CVD patients (Vanhees, Fagard, Thijs, Staessen, and Amery, 1994). While improvements in VO_2 demonstrates an important benefit obtained through HIIT adoption, other studies have found a myriad of potential physiological advantages with HIIT. Research evidence suggests that these HIIT apply to patients with stents, heart attacks, and congestive heart failure (CHF) (Gomes-Neto et al., 2017).

What's more, HIIT potentially improves physiologic outcomes which can impact other chronic diseases treated in cardiac rehabilitation. The chronic disorders that fall under the umbrella of diseases that HIIT can ameliorate include diabetes mellitus (DM), pulmonary disorders, and metabolic disease. Treating metabolic diseases like diabetes or metabolic syndrome is important because they exacerbate heart disease (Ross, Porter, and Durstine, 2016). Specifically, there is a five to seven-fold increase and a two-fold increase in CVD mortality rate, respectively, from diabetes mellitus (DM) and metabolic syndrome (F. Hu et al., 2001; G. Hu et al., 2004). Worse still, affliction from both diseases in concert with previous CVD seems to further aggravate future CVD risk (Malik et al., 2004). There is current evidence that suggests HIIT provides equivalent or improved benefits compared to MCT prescriptions in COPD, diabetes mellites, and metabolic syndrome (Ross et al., 2016).

Despite the possible benefits to patients, HIIT has yet to be has yet to be extensively integrated into rehabilitation facilities and prescriptive models. Several hindrances seem to be responsible for the prevention the universal adoption of HIIT prescriptions for CVD patients. One

deterrent is a legitimate fear that engaging in vigorous intensity activity is too dangerous for CVD patients. Another barrier is the controversy in research literature about whether HIIT outperforms MCT in various physiological benefits or they equivalent. Finally, researchers have yet to develop a standardized guideline for how HIIT should be incorporated into current CVD prescriptions.

Purpose of Study

The purposes of this study are three-fold. First, the study aims to elucidate which aspects of HIIT protocols are equivalent or superior to MCT in rehabilitation settings. Second, this study examines potential safety aspects pertinent to determining whether the adoption of HIIT in cardiac rehabilitation is feasible. Finally, this study will formulate possible prescription guidelines for the incorporation of HIIT into cardiac rehabilitation.

Significance of this Study

This study aims to provide clinicians with a comprehensive evaluation of the literature on the physiologic benefits and risks of using HIIT.

Limitations and Delimitations

No limitations or delimitations were identified.

Basic Assumptions

The results of this study, including the benefits of HIIT, risks of HIIT, and prescriptive guidelines for using HIIT, should only be applied to patients with known CVD. HIIT prescriptions for other populations may vary from those presented in this paper. The potential risks of engaging

in vigorous exercise are less significant for normal populations than for CVD patients who are at an elevated risk of suffering acute cardiovascular events. Therefore, patients at high risk for cardiovascular events should only engage in vigorous activity under direct medical supervision while patients with moderate cardiovascular risk should obtain physician clearance prior to engaging in vigorous exercise (American College of Sports Medicine, 2013).

Definition of Terms

Adipose Tissue- Stored fat tissue.

Ad-Libitum Energy Intake- Self-selected energy intake.

Aerobic Exercise- Activities that utilize rhythmic and continuous movements with large muscle groups.

Ambulatory Blood Pressure- Blood pressure measured and averaged over a 24-hour period.

Anorexigenic- Factors that trigger a loss of appetite.

Atherosclerosis- A disease where plaques build up in arteries which can lead to reduced blood flow or clots if the plaques break open.

Body Composition- The relative distribution of fat tissue compared to other lean tissues like bone and muscle.

Body Weight- The weight of an organism without accounting for body composition.

Cardiac Arrhythmias- Irregular or abnormal heart rhythms.

Cardiovascular Disease (CVD)- The umbrella term for diseases that involve the heart or blood vessels including hypertension, coronary artery disease, peripheral arterial disease, heart valve or electrical conductivity issues, and congestive heart failure.

Catecholamines- Class of neurohormones which include epinephrine and norepinephrine involved in stress responses.

Central Adaptations- Adaptations to exercise that take place in the heart including increased stroke volume, contractility, and cardiac output resulting in increased VO_2.

Congestive Heart Failure (CHF)- An inability of the heart to pump enough blood to body tissues.

Chronic Obstructive Pulmonary Disease (COPD)- A progressive obstructive lung disease that limits airflow during exhalation.

Coronary Artery Bypass Graft (CABG)- A surgical procedure where narrowed or blocked coronary arteries are bypassed using harvested vessels from other areas of the body and then attached to the heart.

Coronary Artery Disease (CAD)- Typically occurs when arteries in the heart are occluded to varying degrees by atherosclerotic plaques which can reduce blood flow to tissues and possibly lead to heart attacks.

Cystic Fibrosis- A genetic disorder that hampers lung function because of overproduction of mucus and frequent infections.

Diabetes Mellites (DM)- A disease where the body's ability to produce or respond to insulin is diminished.

Diastolic Blood Pressure- The arterial pressure when the heart is relaxed.

Dyslipidemia- Characterized by having chronically low HDL cholesterol levels, high triglycerides, or high LDL cholesterol which can contribute to atherosclerosis.

Dyspnea- Difficult or strenuous breathing often because of physical exertion.

Eccentric Contractions- Force producing muscle contractions where the muscle lengths rather than shortens.

Ejection Fraction (EF)- The percentage of blood that leaves the heart when it contracts.

End-diastolic Volumes (EDV)- The volume of accumulated blood in the ventricles at the end of the filling phase (diastole) directly before the ventricles contract.

End-systolic Volumes (ESV)- The volume of remaining blood in the ventricles following contraction (systole) before the ventricles begin to refill.

Endothelial Function- Measurement of vessel's ability to undergo vasodilation, via beta-2 receptors, in response to relaxing factors such as nitric oxide.

Excess Post-Exercise Oxygen Consumption- Elevated oxygen consumption following exercise due to glycogen resynthesis, lactate removal, the catecholamine related elevation of metabolism and lipolysis, the thermic effect of exercise, and increased protein turnover.

Glut 4- An intracellular glucose transporter stimulated to travel to the cell membrane by insulin or exercise.

Glycated Hemoglobin (Hb A1c)- A type of hemoglobin that indicates glucose regulation over a three-month period.

Glycemic Control- Regulation of the bodies blood glucose levels.

Glycogen- The body's form of stored carbohydrates found intracellularly or in the liver.

Heart Rate Recovery- The rate that your heart returns to its idiopathic resting pace.

Heart Rate Reserve- A method of prescribing intensity which first subtracts a subject's resting heart rate from their maximum leaving only a range that occurs during exercise.

Heart Rate Variability- Variation between the intervals of heart beats

Health-Belief Model- A psychosocial model that attempts to elucidate and forecast people's behaviors.

High-intensity Interval Training (HIIT)- Exercise format where the individual alternates between periods of very high intensity and much lower intensity or rest during the workout.

High-risk Individuals- Those with CVD symptoms or diagnosed disease should only engage in vigorous activity under medical supervision.

Hypertension- Chronically elevated blood pressure.

Kaplan-Meier Curves- A method used to predict survival rates in a population.

Lactic Acid- A metabolic byproduct of strenuous or intense exercise which leads to lowered blood pH and elevated breaths rates.

Left Ventricular (LV)- Refers to the largest chamber of the heart responsible for pumping oxygenated blood to the bodies tissues.

Lipolysis- The breakdown and release of fatty acids through hydrolysis.

Maximal Cardiorespiratory Fitness Test- A test that allows researchers to assess a subject's maximal endurance capacity by determining their VO_2 peak.

Metabolic Equivalents (METs)- A measure of the absolute oxygen requirement necessary to do any activity. One MET is the amount of oxygen needed at rest and each MET above that is a multiple of this requirement. (1 MET=rest, 2-3 METs= average walking pace on flat ground, 4 METs= fast walking, 7-8 METs= jogging or a slow run, 10-15 METs= moderate to fast run).

Metabolic Syndrome- A clustering of risk factors that increase the risks for certain CVDs such as heart disease and stroke. Involves concentrated abdominal obesity, dyslipidemia, hypertension, and insulin resistance.

Mitochondrial Biogenesis- The process of mitochondrial mass expansion.

Moderate-intensity Continuous Training (MCT)- Exercise format where the individual increases intensity to a static moderate range of intensities for at least ten minutes.

Moderate Intensity Exercise- Categorized as exercise between 3.0-5.9 METs. Fitness variability also applies to moderate exercise classifications.

Moderate-risk Individuals- Those with two or more CVD risk factors such as age, tobacco use, or sedentary lifestyle among others. These individuals should only engage in vigorous intensity exercise following consultation with their physician.

Myocardial Infarction (MI)- The medical term for a heart attack where clots or plaques completely occlude blood flow to the areas of the heart causing damage or death of tissue.

Orexigenic- A factor that stimulates appetite.

Oxidative Status/Stress- An imbalance between the production of reactive oxygen species and the body's ability to neutralize free radicals.

Peak Oxygen Uptake (VO_2 Peak)- The bodies maximal ability to utilize oxygen in the process of converting fuel stores into usable energy to complete work. VO_2 peak is used in populations with disease because these populations often can't reach a true VO_2 max due to symptomatic limitations, exercise discomfort, or musculoskeletal injury. VO_2 peak instead takes the highest VO_2 achieved during the last stage of an exercise test.

Percutaneous Coronary Intervention (PCI)- A non-surgical procedure where a tube tipped with a balloon is fed into narrowed coronary arteries and then inflated to push the plaque against the vessel wall.

Peripheral Adaptations- Adaptations to exercise that occur within muscle tissue leading to increased VO_2 including capillary density, mitochondrial density, and enzymatic activity.

Ratings of Perceived Exertion- A subjective measurement of the total body intensity of a workout.

Reactive Oxygen Species- Unstable oxygen molecules that can negatively react with other molecules within the body.

Restenosis- The return of an artery to a narrowed state following a corrective surgery.

Sarcopenia- The age-related loss of muscle mass.

Systolic Blood Pressure- The arterial pressure when the heart is contracting.

Socio-ecological Model- A theoretical framework to describe how environmental and personal factors interact to determine behavior.

Stent- Mesh tubes that can be included in PCIs which are often medicated and help to keep vessels open.

Ventricular Remodeling- Changes to the function, shape, or size of the heart's ventricles because of either exercise or injury.

VO_2 Reserve- A method of prescribing exercise intensity that first subtracts out the resting VO_2 leaving a range that covers VO_2 values found during exercise.

Vigorous Exercise- Categorized as exercise above 6 METs. There is variability, however, for what is considered vigorous exercise due to fitness levels, medications that affect fitness, and disease.

Literature Review

The Benefits of HIIT Versus MCT

Peak oxygen consumption and mortality. There have been numerous investigations into the different physiologic changes elicited under HIIT prescriptions. The most recognized change is the improvement of the body's maximal capacity to utilize oxygen (VO_2 peak). VO_2 peak is an important indicator of the body's ability to distribute and utilize oxygen to convert fuel substrates such as glucose or triglycerides into a usable energy source for our cells.

While most research demonstrates that HIIT protocols produce significantly increased VO_2 peak values compared to MCT protocols, there is some incongruity in the data. Various studies using HIIT with patients who have stable coronary artery disease (CAD) elicited greater increases in VO_2 compared to MCT (Rognmo, Hetland, Helgrud, Goff, and Slordahl., 2004; Cardozo, Oliveira, and Farinatti, 2015; Jaureguizar et al., 2016). HIIT's improvements to total cardiorespiratory fitness also applies to patients with other forms of CVD as well. Patients recovering from heart attacks, also called myocardial infarctions (MI), those recuperating from coronary artery bypass graft surgery (CABG), and those with CHF could all potentially benefit from HIIT prescription (Moholdt et al., 2012; Moholdt et al., 2009; Wisloff et al., 2007).

There have also been several meta-analyses on this topic. One meta-analysis by Pattyn, Coeckelberghs, Buys, Cornelissen, and Vanhees (2014) examined nine studies comparing VO_2 values in CAD subjects following an exercise intervention found that HIIT elicited elevated VO_2 peak values compared to MCT (~1.60 $mL \cdot kg^{-1} \cdot min^{-1}$). The findings in the Pattyn et al. study have been supported by other, more recent meta-analyses. One conducted by Elliott, Rajopadhyaya, Bentley, Beltrame, and Aromataris (2015) showed a significant mean difference in VO_2 peaks

(~1.53 $mL \cdot kg^{-1} \cdot min^{-1}$) between the two protocols. While another study by Liou, Ho, Fildes, and Ooi (2016) demonstrated a similar improvement in VO_2 peaks (~1.78 $mL \cdot kg^{-1} \cdot min^{-1}$) with HIIT protocols. In fact, VO_2 peak improvements have also been in CHF meta-analyses. One by Haykowsky et al. (2013) found a significant weighted mean difference in favor of HIIT of about 2.14 $mL \cdot kg^{-1} \cdot min^{-1}$.

In contrast to the studies that demonstrate benefits of HIIT, however, there are other investigations that show nonsignificant differences between HIIT and MCT protocols in CVD subjects (Warburton et al., 2005; Currie, Dubberley, McKelvie, and MacDonald, 2013; Conraads et al., 2015; Pattyn et al., 2016). Recently, a meta-analysis by Gomes-Neto et al. (2017) showed that HIIT protocols elicit higher VO_2 values in many studies, but these improvements disappear when HIIT and MCT caloric expenditures are equalized. Equalized caloric protocols, or isocaloric protocols, demonstrate that energy expenditure, and not exercise intensity, is the main factor behind increases in VO_2 (Gomes-Neto et al., 2017). This elevated importance of energy expenditure further is supported by Vromen et al. (2016) who compared various factors responsible for VO_2 increases in CHF subjects and found that caloric expenditure is more impactful than intensity.

The motivation behind evaluating a protocol's ability to improve VO_2 in CVD patients involves mortality. VO_2 peak has a strong correlative relationship with all-cause mortality in the general population. The correlation between VO_2 and mortality holds even after controlling for sex, age, smoking, body composition, fitness test used, or study design (Lee, Artero, Sui, and Blair, 2010). Of equal importance though, VO_2 peak is highly prognostic of cardiovascular mortality both with CAD and CHF (Vanhees et al., 1994; Cahalin et al., 2013).

There is a reduction of between 13-22% in overall mortality risk with each metabolic equivalent (MET) increase (Martin et al., 2013). For those individuals classified as low fitness (less than five MET peak capacity), increasing their total MET capacity by one MET reduces their overall mortality risk by up to 30% (Martin et al., 2013). Improvements in mortality risk are further bolstered by survival analyses utilizing Kaplan-Meier curves which illustrate that initial fitness levels increase survival even when adjusted for factors like comorbidities, treatments, and disease severity (Martin et al., 2013). This connection between VO_2 peak and mortality forms the cornerstone of arguments supporting HIIT implementation in rehabilitation programs.

VO_2 peak isn't the only variable improved by HIIT protocols that influence cardiovascular mortality though. There is evidence that both heart rate recovery speed and heart rate variability are associated with cardiovascular mortality as well (Nishime, Cole, Blackstone, Pashkow, and Lauer, 2000; La Rovere, Bigger, Marcus, Mortara, and Schwartz, 1998). Studies comparing HIIT to MCT while examining heart rate recovery and variability have shown that HIIT significantly improves these variables (Munk, Staal, Butt, Isaksen, and Larsen, 2009; Moholdt, Bekken Vold, Grimsmo, Slordahl, and Wisloff, 2012; Kiviniemi et al., 2014). At least one study, however, has demonstrated that HIIT isn't superior to MCT at improving heart rate recovery and variability (Currie, Rosen, Millar, McKelvie, and MacDonald, 2013).

Mitochondrial biogenesis. The exact mechanisms behind why HIIT's ability to stimulate VO_2 improvements are still poorly understood (Hussain, Macaluso, and Pearson, 2016).
Some lines of evidence, however, suggest that the factors triggering HIIT's VO_2 improvement beyond MCT are peripheral rather than central **(**MacPherson, Hazell, Oliver, Paterson, and Lemon, 2011). A propensity for the development of peripheral adaptations translates to a likelihood that

HIIT elicits changes in factors like mitochondrial density and capillarization (a-vO2 difference) rather than maximum cardiac output or stroke volume (MacPherson et al., 2011).

Mitochondrial density represents an intriguing reason for why HIIT might outperform MCT at improving VO_2. HIIT protocols are connected to mitochondrial density through an intracellular fuel biosensor protein called adenosine monophosphate-activated protein kinase (AMPK), which is upregulated during HIIT protocols (Gibala et al., 2009). Several studies have shown that HIIT protocols upregulate AMPK more than MCT (Tjonna et al., 2008; Wisloff et al., 2007; Gibala, Little, Macdonald, and Hawkley, 2012). AMPK then works in concert with another protein, which is also upregulated by HIIT, called p38 mitogen-activated protein kinase (p38 MAPK) to activate a molecule called PGC-1α, which stimulates mitochondrial biogenesis (Jager, Handschin, St. Pierre, and Spiegelman, 2007; Gibala et al., 2012). PGC-1α is activated by AMPK and p38 MAPK through phosphorylation, which is the process of adding a phosphoryl group to PGC-1α (Gibala et al., 2012). Once activated, PGC1-α is thought to be a key regulator of mitochondrial gene transcription in the cell, although a recent review by Islam, Edgett, and Gurd (2018) argues PGC-1α's actual role is more nuanced than being a master regulator of mitochondrial biogenesis (Serpiello et al., 2012). Regardless of this debate though, increases in PGC1-α seem to influence oxidative capacity, anti-oxidant defense, glucose uptake, resistance to sarcopenia, and inflammation (Benton et al., 2008; Sandri et al., 2006; Wenz, Rossi, Rotundo, Spiegelman, and Moraes, 2009). The exact process of how PGC1-α and AMPK trigger mitochondrial biogenesis is beyond the scope of this review. Palikaras and Tavernarakis (2014) have conducted a more thorough review of the interplay between PGC1-α, AMPK, and mitochondrial biogenesis

Vascular benefits. There is evidence that long-term disturbances in vascular homeostasis like hypertension or dyslipidemia can be risk factors for the development of CVD (Fornoni and

Raij, 2005). These risk factors can also be exacerbated by other vascular factors like increased oxidative status or by changes in endothelial function (Muniyappa and Sowers, 2013). Exercise has demonstrated a capability to restore vascular homeostasis by improving endothelial function and by improving CVD risk factors like hypertension (Joyner and Green, 2009; Ignarro, 2002).

Hypertension, or persistent high blood pressure, and its connection to CVD is particularly insidious. The serious nature of hypertension is demonstrated by an increased incidence of CVD beginning at blood pressures as low as 115/75 mm Hg which doubles with each 20/10 mm Hg increase (Chobanian et al, 2003). Fortunately, acute aerobic exercise has been shown to reduce ambulatory blood pressure for up to 24 hours following an exercise session in hypertensive patients (Ciolac et al., 2008; Pescatello & Kulikowich, 2001). Exercise induced improvements are typically elicited with MCT protocols along in conjunction medications and dietary changes (Haskell et al., 2007).

In theory, HIIT should improve blood pressure more than MCT. Studies indicate that those with a higher cardiorespiratory fitness level (VO_2 peak) have a lower incidence of hypertension than their less fit peers (Barlow et al., 2006; Blair, Goodyear, Gibbons, and Cooper, 1984; Carnethon et al., 2003). One study by Carnethon et al. (2003) exhibited that there would be a 21% reduction in hypertension if low fit individuals increased their fitness levels. As discussed earlier, HIIT is thought to be more efficacious at improving VO_2 peak than MCT and at least two studies in hypertensive patients, or those at familial risk for hypertension, have demonstrated this as well (Ciolac, Bocchi, Greve, and Guimaraes, 2011; Tjonna et al., 2008). Though more studies investigating long-term effects of HIIT on blood pressure are necessary to solidify our understanding of the link between HIIT and hypertension.

Another area where HIIT prescriptions should theoretically help improve blood pressure more than MCT deals with arterial stiffness, which is commonly measured by pulse wave velocity (PWV). Arterial stiffness increases with aging and is typically greater in individuals with hypertension (Benetos et al., 2002). Furthermore, individuals with a familial risk for hypertension have shown increases in PWV and arterial stiffness prior to increases in blood pressure (Ciolac et al., 2010a; Ciolac et al., 2010b; Kucerová et al., 2006). PWV is also pertinent because central arterial stiffness is a predictor of both cardiovascular and all-cause mortality (Laurent et al., 2001). Fortunately, regular aerobic exercise has the potential to attenuate worsening arterial stiffness, and aerobic exercise can both lower the risk of hypertension in normotensive patients and decrease blood pressure in those who already have hypertension (Tanaka et al., 2000; Blair SN, Goodyear NN, Gibbons LW, et al., 1984; Barlow et al. 2006; Ciolac EG, Guimarães GV, D'Avila VM, et al., 2008). HIIT is relevant because it has demonstrated that it can reduce PWV and thus arterial stiffness more than MCT after a 16-week period (Ciolac et al., 2010b; Guimaraes et al., 2010)

There is still a question in the literature, however, of whether HIIT has the potential to directly influence blood pressure more than MCT. On one hand, there are two studies that demonstrate greater reductions in blood pressure with HIIT protocols (Tjonna et al., 2008; Molmen-Hansen et al., 2012). One study by Molmen-Hansen et al. (2012) determined that HIIT improved systolic but not diastolic ambulatory blood pressures more than MCT following 12 weeks of training. The other study by Tjonna et al. (2008) showed the opposite with improvements in diastolic but not systolic pressures in a similar 12-week period. On the other hand, there have been studies showing that HIIT and MCT result in equal reductions in blood pressure. Wisloff et al. (2007) demonstrated this when they found no significant differences in blood pressure in CHF patients after 12 weeks of HIIT or MCT training. These results were supported Schjerve et al.

(2008), who found no blood pressure differences between HIIT and MCT groups in obese patients after a 12-week period.

Like hypertension, dyslipidemia, or an a chronically elevated blood lipid profile, has a direct effect on the occurrence of CHD (Lloyd-Jones et al., 2004). For example, prolonged exposure to elevated lipid levels is capable of damaging endothelial cells in vessels (Cersosimo,. and DeFronzo, 2006). Blood lipids are also an integral part of the atherosclerotic plaque formation process (Hansson and Hermansson, 2011). Aerobic exercise seems to have a significant but small effect on blood lipid profiles with at least a 12- week training program (average of 4.6% HDL cholesterol increase, 3.7 % triglyceride levels decrease, and 5 % LDL cholesterol decrease) (Leon & Sanchez, 2001). More specifically, studies show that moderate-intensity exercise is better at improving HDL cholesterol while high-intensity improves LDL cholesterol and triglycerides (Mann, Beedie, and Jimenez, 2014).

But more importantly, HIIT shows potential at improving vascular oxidative status more than MCT (Wisloff et al., 2007). The mechanisms behind this improvement is thought to be upregulation of nitric oxide (NO) and glutathione peroxidase following intense interval exercise (Tjonna et al., 2008; Mitranun, Deerochanawong, Tanaka, and Suksom, 2014). Both NO and glutathione have been shown to reduce levels of reactive oxygen species (ROS) and improve oxidative status (Chakraphan et al., 2005; Lubos, Loscalzo, and Handy, 2011). The neutralization of ROS by endogenous antioxidants is important because increases in ROS factors into the formation of oxidized LDL, which has been implicated in the progression of a variety of cardiovascular diseases (Trpkovic et al., 2015). Studies that test for oxidized LDL have found lower levels subsequent to HIIT when compared to MCT protocols (Tjonna et al., 2008; Wisloff et al., 2007; Schjerve et al., 2008).

Finally, there is one additional area indicative of vascular homeostasis that HIIT has shown the potential to improve. Endothelial function is a critical mechanism for the control of vascular homeostasis because it is indicative of the body's ability to change vessel diameter in response to endothelium constricting or relaxing factors (Matsuzawa and Lerman, 2014). Endothelial responsiveness can be disrupted by cardiovascular risk factors like tobacco use or hypertension which proliferates factors that lead to vessel constriction (Matsuzawa and Lerman, 2014). Persistent vessel constriction can lead to accelerated atherosclerosis and the development of CVD (Matsuzawa and Lerman, 2014). Endothelial dysfunction can be reversed, however, when endothelial cells are induced to upregulate NO production, which is one of the most potent vasodilators (Ramos, Dalleck, Tjonna, Beetham, and Coombes, 2015).

As previously established in this review, HIIT elicits an increased production of NO compared to MCT protocols (Tjonna et al., 2008; Mitranun, Deerochanawong, Tanaka, et al., 2014). Furthermore, a meta-analysis by Ramos et al. (2015) of studies comparing the two exercise protocols found a significant improvement in a measure of vascular function called flow-mediated dilation (FMD) (mean difference of 2.26%). The advantage in FMD is important for individuals with CVD because increases of just 1% FMD can reduce the risk of cardiovascular events by 13% (Inaba, Chen, and Bergmann, 2010). HIIT's advantage at improving vascular function may not exist with all types of high-intensity protocols, however. A study investigating high-intensity continuous training found no significant differences in vasodilation compared to MCT (Goto et al., 2003). These findings are supported by studies that found increased levels of ROS and fewer antioxidants following high-intensity exercise (Davies, Quintanilha, Brooks, and Packer, 1982; Bergholm et al., 1999). The shift in oxidative stress suggests that there is a threshold for high-intensity exercise where NO production declines (Goto et al., 2003). HIIT, however, may be able

to overcome this disadvantage due to its reduced duration at high-intensities compared to continuous protocols (Ramos et al., 2015).

Cardiac specific benefits. HIIT appears to offer CVD patients several cardiac specific benefits. For one, in patients who have undergone a percutaneous coronary intervention and stent implantation, HIIT improved endothelial function and inflammation as measured by a key marker call C-reactive protein (Munk et al., 2009). HIIT's effect on inflammation, along with improved aerobic fitness levels, are associated with a reduction in late luminal loss around the stinted area which is indicative of the risk of restenosis (Munk et al., 2009). Additionally, in subjects with CHF, HIIT can elicit improvements in left ventricular remodeling, LV end-diastolic and end-systolic volumes, ejection fraction, and pro-brain natriuretic peptide all of which are important dependent outcomes (Wisloff et al., 2007). Studies displaying HIIT's effect on ventricular remodeling have been supported by a meta-analysis which showed that HIIT improves both LV ejection fraction and LV end-diastolic diameter more significantly than MCT (Cornelis, Beckers, Taeymans, Vrints, and Vissers, 2016). Another study in CHF patients found that HIIT was able to reduce premature ventricular contraction arrhythmias (Guiraud et al., 2013).

Positive findings using HIIT with CHF may not be incontrovertible though. One recent study with a large sample size (n=261) showed no difference in LV end-diastolic diameter between HIIT and MCT protocols (Ellingsen et al, 2017). Furthermore, as with improvements in V_{O2} peak, there is research indicating that improvements in hemodynamics, ejection fraction, and cardiac parasympathetic regulation disappear when protocols are matched to be isocaloric (Iellamo et al., 2013a; Iellamo et al., 2013b).

Weight and appetite. Obesity is an independent risk for CVD (Bastien, Poirier, Lemieux, and Despres, 2014). But obesity also impacts overall CVD risk by negatively modulating other

risk factors like dyslipidemia, hypertension, DM, glucose intolerance, and overall inflammatory state (Bastien et al., 2014). These factors significantly increase the risk of all-cause mortality (Flegal, Kit, Orpana, and Graubard, 2013). Thus, reducing obesity should be a top priority of any program aiming to mitigate the risk of CVD development and prevention. Exercise represents a moderately effective strategy that, when combined with more effective strategies like a hypocaloric diet, can help to reduce total body weight and improve body composition (Wewege, van den Berg, Ward, and Keech, 2017). HIIT can also benefit weight loss through several mechanisms including elevated excess post-exercise oxygen consumption (EPOC), post-exercise appetite suppression, and direct caloric expenditure.

EPOC is a description of the post-exercise oxygen consumption necessary to restore the body to metabolic homeostasis (LaForgia, Withers, and Gore, 2006). Researchers theorize that the specific mechanisms responsible for EPOC are glycogen resynthesis, lactate removal, the catecholamine related elevation of metabolism and lipolysis, the thermic effect of exercise, and increased protein turnover in muscles (Hazell, Olver, Hamilton, and Lemon, 2012). Exercise intensity seems to have a direct effect on the magnitude and duration of EPOC while exercise duration seems to correlate only with EPOC duration (Hazell et al., 2012). Intensity-dependent changes in EPOC explain why high-intensity protocols elicit similar oxygen consumption values over a 24-hour period as moderate-intensity protocols in less than a tenth of the exercise time (Hazell et al., 2012). These increases in EPOC with HIIT endure even when prescriptions are designed to be isocaloric with MCT protocols (LaForgia et al. 2006). An elevated EPOC from HIIT can contribute small increases to caloric expenditure over a single day, but these expenditures add up to only 3 extra pounds of adipose tissue loss over the course of a year (LaForgia et al., 2006). Over short periods of time, HIIT protocols have little effect on weight loss, but if HIIT is

incorporated into a long-term weight loss regimen, the protocol can have a measurable effect on weight maintenance.

On top of HIIT's modest improvements of post-exercise caloric expenditure, the exercise strategy can also benefit individuals attempting to lose weight by reducing ad-libitum energy intake (self-selected food consumption) (Sim, Wallman, Fairchild, and Guelfi, 2014). Importantly, HIIT seems to induce appetite suppression beyond what is observed with MCT and these changes can last over 24-hours (Sim et al., 2014). The mechanisms behind HIIT induced appetite suppression stem from changes in orexigenic (appetite stimulating) and anorexigenic (appetite suppressing) signals and hormones. HIIT impacts orexigenic signals by triggering gastric blood redistribution, circulating catecholamines, and elevated body temperatures (Hazell, Islam, Townsend, Schmale, and Copeland, 2016). Similarly, HIIT protocols upregulate anorexigenic signals by releasing cytokines like IL-6, increasing gastric mobility, and amplifing concentrations of blood lactate and blood glucose (Hazell et al., 2016). Both appetite regulation processes are modulated in an intensity dependent manner (Hazell et al., 2016).

Though HIIT has advantages over MCT in post-exercise caloric expenditure and intake, these differences are not reflected in studies investigating the effect that the protocols have on body composition, waste circumference, and total weight loss. To begin with, a meta-analysis by Liou et al. (2016) investigating body weight changes following either HIIT or MCT protocols in CVD participants found that HIIT elicited inferior body weight changes. Other meta-analyses have found equivalent improvements with body adiposity and waist circumference between the two protocol types (Keating, Johnson, Mielke, and Coombes, 2017; Wewege et al., 2017). HIIT, however, may be able to accomplish these equivalent improvements with a 40% reduction in time commitment, though this is in dispute (Wewege et al., 2017; Keating et al., 2017).

Adherence and quality of life. There is one additional area where the incorporation of HIIT prescriptions could benefit CVD patients. One major reason that adults give for not adhering to a regular exercise regime is lack of time (Trost, Owen, Bauman, Sallis, and Brown, 2002). According to a study by Gibala et al. (2006), HIIT protocols can elicit similar benefits as MCT with around 20% of the duration. Furthermore, this time efficiency and the dynamic nature of HIIT protocols have corresponded to elevated enjoyment despite being perceived as more physically demanding (Bartlett et al., 2011; Thum, Parsons, Whittle, and Astorino, 2017). HIIT's dynamic and efficient nature helps to explain why it improves exercise adherence more than MCT. A study conducted by Moholdt et al. (2011) found that long-term adherence improved in HIIT subjects compared to MCT group subjects. The findings by Moholdt et al. (2011) have been supported by Aamot, Karlsen, Dalen, and Stoylen (2016) who found that subjects from a HIIT group had very high levels of adherence according to self-reported surveys.

While there is evidence of HIIT's superiority over MCT with exercise adherence, there is little to no evidence reflecting similar improvements with quality of life (QoL). One study has shown that HIIT improves the QoL of CHF subjects, but the HIIT results were only compared with a usual care group and a no exercise advice group (Chrysohoou et al., 2014). Another study evaluated QoL with both HIIT and MCT found that both improved QoL but found no significant differences between the protocols were identified (Jaureguizar et al, 2016). HIIT's neutral effect on QoL compared to MCT is supported by meta-analyses on both CHD and CHF subjects showing equivalent improvements in QoL after the protocols (Cornelis, Beckers, Taeymans, Vrints, and Vissers, 2016; Gomes-Neto et al., 2017). It should be noted, however, that both meta-analyses only included two studies on QoL. Thus, more research on the subject needs to be conducted to elucidate differences in QoL between HIIT and MCT protocols.

Other Chronic Diseases

Pulmonary benefits. Rehabilitation facilities often assist patients with pulmonary disorders in improving or maintaining their QoL alongside cardiac patients. Pulmonary rehabilitation is frequently used to treat chronic obstructive pulmonary disease (COPD) and occasionally other pulmonary disorders such as asthma, interstitial lung disease, cystic fibrosis, or pulmonary hypertension (Sharma and Singh, 2011). Pulmonary rehabilitation exercise programs facilitate improvements in functional exercise capacity, dyspnea, QoL, fatigue, and emotional function (Lacasse, Martin, Lasserson, and Goldstein, 2007).

High-intensity exercise offers COPD patients with potentially superior benefits (Casaburi et al., 1991). The issue is, COPD patients are often unable to sustain these high-intensities for the prescribed duration before they succumb to fatigue (Punzal, Ries, Kaplan, and Prewitt, 1991). However, COPD patients may tolerate extended exercise at high-intensity with HIIT because it produces smaller increases in arterial lactic acid concentrations (Casaburi et al., 1991). This reduction in lactic acid helps to reduce carbon dioxide produced by the body's bicarbonate buffering system and thus reduces the stimulus to breath (Brooks, Fahey, and Baldwin, 2007; Sabapathy, Kingsley, Schneider, Adams, and Morris, 2004). In fact, a study by Vogiatzis et al. (2004) found that interval training allowed patients with severe COPD to exercise at a high intensity (100% work rate max compared to 80%) for up to three times longer than continuous exercise, but with lower ventilatory responses. Lower dyspnea ratings and leg discomfort seem to be the main advantages of HIIT training over MCT in COPD patients and these benefits also apply to prospective lung transplant patients (Vogiatzis et al., 2005; Gloeckl, Halle, and Kenn, 2012). HIIT protocols also benefit asthma patients in asthma control, dyspnea, and QoL (da Silva et al., 2016a; da Silva 2016b). However, there are no significant differences with HIIT in COPD patients

in other variables like V_{O2} peak, exercise capacity, and QoL when compared to MCT (Arnardóttir, Boman, Larsson, Hedenström, and Emtner, 2007).

Diabetes benefits. Diabetes is a chronic disease that can aggravate the risk for CVD development (Sawar et al., 2010). Even after other risk factors like age, sex, smoking, systolic blood pressure, and body-mass index are accounted for, diabetes can increase the risk of developing vascular diseases by a factor of two (Sawar et al., 2010). Those who engage in regular physical activity, however, can reduce their risk of developing type-two DM by up to 50% (Helmrich, Ragland, and Leung, and Paffenbarger, 1991). What's more, even a single bout of exercise can confer improved insulin sensitivity for up to 48 hours leading to improved glycemic control in type-two DM (Devlin, Hirshman, Horton, and Horton, 1987).

While moderate-intensity exercise is beneficial for type-two DM, there is evidence that exercise intensity is more influential on glycemic control compared to exercise volume (Boulé, Haddad, Kenny, Wells, and Sigal, 2001). One possible reason for improved glycemic control with vigorous intensity exercise involves the link between mitochondrial impairment and insulin resistance (Szendroedi, Phielix,. and Roden, 2011). As previously established in this review, HIIT has the potential to upregulate mitochondrial density which has been shown to improve insulin signaling (Hesselink, Schrauwen-Hinderling, and Schrauwen, 2016). Another possible reason HIIT improves glycemic control could involve the protein glucose transporter GLUT4. GLUT4 is an intracellular transporter that translocates to the cell membrane in response to both insulin or acute exercise; this translocation process is involved in glucose homeostasis (Kalhor, Peeri, Homaee, and Izadi, 2017). HIIT has been shown to outperform MCT in eliciting significantly larger increases in GLUT4 content in diabetic mice thus aiding glucose metabolism (Chavanelle et al., 2017).

HIIT also has the potential to influence GLUT4 transporters, and thus glycemic control, through insulin sensitivity. HIIT protocols demonstrate the ability to increase insulin sensitivity in both liver and adipose tissues in diabetic mice (Marcinko et al., 2015). However, improvements in insulin sensitivity have not translated to humans when oral glucose tolerance tests are used (Schjerve et al, 2008). But when homeostatic model assessment-insulin resistance tests are utilized, there is a significant improvement in insulin sensitivity with HIIT compared to MCT (Tjonna et al., 2008; Mitranun et al., 2014). Furthermore, HIIT maintains these improvements even when healthy, diabetic, obese, and other chronic disease populations are included (Jellyman et al., 2015).

While improvements in insulin sensitivity can be positively impactful for those who have type two DM, it can be important to physiological measures of glucose homeostasis to ascertain if a protocol is helping to treat the underlying disease. Testing for glycated hemoglobin A1c (HbA1c) is the current gold standard for measuring glucose regulation and is endorsed by the American Diabetes Association as a diagnostic test (Cox and Edelman, 2009; Gillett, 2009). Two studies investigating HbA1c changes following either HIIT or MCT protocols found differing results. One by Schjerve et al. (2009) found no changes between protocols in HbA1c while another by Mitranun et al. (2014) found a significant improvement with HIIT. Both studies had similar protocols lasting 12 weeks and having subjects exercise three times each week (Schjerve et al., 2009; Mitranun et al, 2014). Though more research needs to be conducted on the issue, a meta-analysis by Jellyman et al. (2015) did not find any significant effect of HIIT on HbA1c compared to MCT.

HIIT Safety

One of the most crucial concerns for clinicians deciding whether to incorporate HIIT prescriptions into their programs involves safety. According to the American College of Sports Medicine's, *Guidelines for Exercise Testing and Prescription* (2013), HIIT falls under the category of vigorous exercise. Vigorous exercise raises the risk of MI and sudden cardiac death in prone individuals (Siscovick, Weiss, Fletcher, and Lasky, 1984; Albert et al., 2000). For these reasons, it is vital that clinicians exercise caution when selecting patients for HIIT protocols and that patients follow exercise guidelines when using HIIT. Guidelines generally state that moderate-risk individuals should obtain physician clearance before engaging in vigorous activity and that high-risk individuals should only participate in vigorous activity while under medical supervision (ACSM, 2013).

Professionals should evaluate safety concerns when selecting patients who might benefit from HIIT, but these concerns shouldn't preclude practitioners from adopting HIIT protocols when the benefits outweigh the risks. This recommendation is based on an extensive study on the safety aspects of high-intensity in cardiac rehabilitation facilities conducted by Rognmo et al. (2012). In the Rognmo et al. (2012) report, researcher followed nearly 5000 patients in three rehabilitation facilities over seven years looking for adverse acute cardiovascular events. Investigators found the rates of adverse events to be one in 130,000 hours of moderate-intensity activity and one in 23,000 hours for high-intensity activities. One key note, however, was that the adverse events recorded in this report were cardiac arrests and most patients were resuscitated. The low rates of cardiac events found in the Rognmo et al. (2012) study only apply to medically supervised exercise programs where rapid cardiac medical treatment is available. It is estimated that rates of adverse events are six times higher outside medically supervised programs (Rognmo et al., 2012). The relative risks

of other adverse occurrences with MCT are: one major complication for every 90,000 patient hours, one MI every 220,000 patient hours, and one fatality every 750,000 patient hours in contemporary rehabilitation settings (Rognmo et al., 2012). Though more research needs to be conducted to discover more exact adverse event rates for high-intensity, established complication rates for moderate-intensity exercise suggests that severe adverse events, such as MI or fatalities, may be less common than cardiac arrests for high-intensity activity as well.

Another area of risk when considering whether to adopt HIIT protocols may be an increased risk of musculoskeletal or orthopedic injury. Concerns with exercise-related injuries arise with HIIT due to changes in muscle and tendon properties that coincide with increasing age. Tendons lose stiffness with age while muscle generates less force and power due to sarcopenia, which is the age-related loss of muscle mass (Stenroth, Peltonen, Cronin, Sipila, and Finni, 2012). These changes in tendon and muscle properties may be partially responsible for increased muscle damage following eccentric contraction in older mice (Choi, 2016). However, the relationship between age and muscle injury in humans is still unsettled, however (Choi, 2016). Furthermore, tendon seems to be able to compensate for losses in stiffness by increasing cross sectional area (Stenroth et al., 2012).

Finally, there is a debate on whether exercise intensity can impact the incidence of exercise injury. Numerous studies have found a positive relationship between intensity and running-related injury, but just as many investigations found no link between the variables (Nielsen, Buist, Sorensen, and Lind, 2012). One study, however, found that interval training can increase the risk of shin injuries during running (Wen, Puffer, and Schmalzried, 1998). In contrast, a study by Carl et al. (2017) on HIIT safety with chronic stroke patients found no increase in orthopedic injury. Despite the ambiguity of whether age and intensity can predispose a person to injury when

practicing HIIT, practitioners need to carefully consider previous orthopedic injury and preferably include orthopedic screening. Additionally, this uncertainty about the relationship between HIIT and injury warrants further investigation or if possible a meta-analysis of existing studies.

HIIT Programming

To maximize positive outcomes for patients, rehabilitation professionals need to follow established exercise prescription guidelines. These guidelines include consideration of exercise frequency, intensity, type of exercise, and total exercise time as well as volume and progression (ACSM, 2013). HIIT protocols, however, add additional layers of complexity to the prescription process. When prescribing these protocols, professionals must also consider the intensities of the work and rest intervals, the durations of each interval type, the number of intervals in a workout, (Buchheit, 2005).

There have been several reviews that have analyzed the HIIT prescriptive variables utilized in CVD studies. These reviews indicate that HIIT protocol periods can range between 2-16 weeks with two to three sessions per week (Ramos et al., 2015; Hussain et al., 2016; Ito, Mizoguchi, and Saeki, 2016) Most studies, however, employ a protocol period last 12 weeks with three sessions per week (Ito et al., 2016). CVD patients have shown the ability to engage in HIIT protocols for total durations of between 20-48 minutes with most protocols lasting 25 minutes (Ribeiro et al., 2017).

With regards to intensity and interval number for both work and rest intervals, there are two schools of thought on what is best for CVD patients. Ribeiro et al. (2017) recommends a paradigm focusing on short intervals (15-30 seconds), with higher intensity (100% VO_2 peak vs 80-85% VO_2 peak), and passive recovery of equal length to the work interval which is better tolerated by subjects. This form of HIIT protocol results in lower ventilation ratings and ratings of

perceived exertion (RPE), more time exercising, and were preferred by patients (Guiraud et al., 2010; Meyer et al., 2012). Importantly, these protocol choices may mitigate gains in VO_2 peak values compared with longer, less intense intervals compared to MCT (Ito et al., 2016).

Researchers that have chosen longer intervals have commonly used four bouts of four-minute-long intervals (4x3 model) at 85-95% max heart rate or VO_2 peak (Hussain et al, 2016). The work intervals of these long interval protocols are interspersed by three-minute active recovery intervals with an intensity typically around 60-70% max heart rate (Hussain et al.,2016). These longer intervals with active recovery periods lower exercise adherence and are less tolerable to patients due to more time spent at vigorous intensities (Guiraud et al., 2010; Guiraud et al., 2012). Furthermore, patients that are extremely deconditioned are unlikely to handle long intervals above 60-70% of maximal intensities (Arena, Myers, Forman, Lavie, and Guazzi, 2013). However, this interval type has been shown by several meta-analyses to be the optimal prescription format for increasing VO_2 and vascular health for subjects (Smart, Dieberg, and Giallauria, 2013; Angadi et al., 2015). The intricacies of how short and long protocol affect subjects suggests that HIIT programs need to be individually tailored to patient preference, initial maximal aerobic capacity, and preferred clinical outcome. Additionally, this review recommends choosing exercise protocols for patients that maximizes total caloric expenditure rather than attempting to maximize time spent near VO_2 peak. Maximum caloric expenditure should be the principal goal of HIIT prescriptions because of evidence suggesting that caloric expenditure is the main factor leading to greater gains in VO_2 (Iellamo et al., 2013a; Iellamo et al., 2013b; Vromen et al, 2016; Gomes-Neto et al., 2017).

Methodology

Review Methodology

A review of the literature related to HIIT was conducted and included only randomly or non-randomly controlled trials that have been submitted to peer-review journals. Abstracts, case reports, and letters to journals were excluded from review.

Research Methodology

The review of literature was organized into four sub categories. The first category is the advantages of using HITT versus MCT for CVD patients. The next is on difference between using MCT and HITT with different chronic diseases. The third category covers HIIT safety issues for older adults and those with CVD. Finally, the last category contains material related to HIIT prescription guidelines to provide safe conditions and maximize outcomes for patients.

Treatment of Research

Information this literature review was used to assess the potential risks and rewards of incorporating HIIT prescriptions into cardiac rehabilitation. The review was also used to develop a literature-based exercise guideline for HIIT prescriptions. This guideline utilized previous research on HIIT program optimization for both chronic populations and healthy populations.

Exercise Prescription

Figure 1. High-intensity interval protocol for patients with coronary heart disease or congestive heart failure incorporating exercise frequency, intensity, time, type, and progression.

Warm up/Cool Down: 5-10 minutes at 40-50% V_{02} peak/ 30-50% Peak Power Output

Patient Functional Capacity

	≤5 METs **Weight Supported Exercise (Cycling)**	**5-8 METs** **Weight Bearing Exercise (Treadmill)**	**8+ METs**
Week (0-4)	HIIT Not Recommended	Type: Short Interval	Type: Medium Interval
Interval Duration		W:15-60 seconds Rec:15-60 seconds	W:1-3 minutes Rec:1-3 minutes
Intensity		W:90%V_{O2} Reserve Rec: Passive Recovery	W:100% V_{O2} Reserve Rec:40-50% V_{O2} Reserve
Session Duration		10-15 minutes	15-30 minutes
Frequency		1x per week	2x per week
Week (4-8)	Type: Short Interval	Type: Medium Interval	Type: Long Interval
Interval Duration	W:10-30 seconds Rec:10-30 seconds	W:1-2 minutes Rec:1-2 minutes	W:4 minutes Rec: 3 minutes
Intensity	W:90% Peak Power Output Rec: Passive Recovery	W:90%V_{O2} Reserve Rec:40-50% V_{O2} Reserve	W: 80-85%V_{02} Reserve Rec:50-70%V_{02} Reserve
Session Duration	10-15 minutes	15-24 minutes	25-35 minutes
Frequency	1x per week	1-2x per week	3x per week
Week (8+)	Type: Medium Interval	Type: Long Interval	Type: Long Interval
Interval Duration	W:1-3 minutes Rec:1-3 minutes	W:4 minutes Rec: 3 minutes	W:4 minutes Rec: 3 minutes
Intensity	W:95% Peak Power Output Rec:50%Peak Power Output	W: 80-85%V_{02} Reserve Rec:50-60%V_{02} Reserve	W: 85-95%V_{02} Reserve Rec:70%V_{02} Reserve
Session Duration	15-24 minutes	25-35 minutes	25-45minutes
Frequency	1-2x per week	3x per week	3x per week

HIIT: High-intensity interval training; METs: Metabolic equivalents W: Work interval; Rec: Recovery interval
This table was adapted from table 1. From Ribeiro et al. (2017) and draws from Warburton et al. (2005); Guiraud et al. (2010); Guiraud et al. 2012; Meyer et al. (2012); Arena et al. (2013); Hussain et al. (2016); and Ito et al. (2016).

Prescription Development

This HIIT protocol was developed to add to the HIIT prescriptive model developed by Ribeiro et al. (2017). Additions to the Ribeiro et al. (2017) protocol include: specific recommendations of warmup and cooldown from Arena et al. (2013), inclusion of another fitness category of eight plus METs, conversion of VO_2 peak intensity prescription to VO_2 reserve, specific exercise durations and possible modalities, and a faster progression towards a 4x3 HIIT model in moderate to high-fitness subjects to facilitate greater physiologic gains (Vromen et al., 2015; Ito et al., 2016). The new fitness category of eight plus was added to capture higher fitness individuals in cardiac rehabilitation and to reflect differences in survival curves based on fitness (Gee, Viera, Miller, and Tolleson-Rinehart, 2014; Martin et al., 2013; Kokkinos et al., 2008). Higher-fit individuals can tolerate a more demanding HIIT protocols and would benefit more from a faster progression to a 4x3 HIIT model. Finally, the intensity prescription was changed from VO_2 peak to VO_2 reserve to account for resting VO_2 use and to align with ACSM guidelines (Swain and Franklin, 2002).

Though HIIT prescriptions should be developed by prescribing intensity with VO_2 peak, but when intensity ranges are given to patients, the intensity needs to be converted to heart rate reserve and ratings of perceived exertion. Conversion of intensity from VO_2 peak or reserve to heart rate percentages will put HIIT intensity in terms that patients can understand and will give them a measure of control if they are provided with a heart rate monitor. Providing patients with heart rate monitors is also important as it has been shown to improve adherence during HIIT protocols (Rognmo et al. 2004). Additionally, patients should be encouraged to participate in both resistance training and aerobic exercise. This combination of resistance and strength training has demonstrated superior improvements in body composition, QoL, muscle strength, and peak work

capacity compared to either training type alone (Gayda et al., 2016). Exercise physiologists should be careful, however, to prescribe a total exercise volume that doesn't exhaust patients and prevent them from having the energy to complete activities of daily living.

Conclusion

The recent attention that HIIT protocols have garnered in cardiac rehabilitation literature appears to be justified. HIIT improves: cardiovascular parasympathetic control, areas of vascular health, cellular and post-exercise metabolism, exercise adherence, discomfort in pulmonary patients, and insulin sensitivity in diabetic patients. Additionally, even if VO_2 peak and ventricular remodeling improvements disappear with isocaloric protocols, HIIT burns more calories than MCT and thus can generate similar improvements with greater efficiency (Falcone et al., 2015; Gibala et al., 2006). In many of the evaluated benefit categories, HIIT was found to be equivalent, if not superior to MCT

In addition to being efficacious, HIIT also seems safe to prescribe to CVD patients. The protocol causes an increase of cardiac arrest rates from 1/130,000 moderate-intensity hours to 1/23,000 high-intensity hours (Rognmo et al., 2012). But even so, observed rates of cardiac arrests are low. For example, if you estimate the number of increased cardiac arrests for MI subjects, the outcome is negligible. Generally, there are around 735,000 MI's each year, of which, roughly 100,000 are enrolled in cardiac rehabilitation (Kachura et al., 2017). If each of these patients completes 26 hours of exercise over their rehabilitation experience (an average of 45 minutes of aerobic exercise over 36 one-hour sessions), then these patients accumulate around 2,600,000 exercise hours. Even if all these hours are performed with HIIT, there would only be an increase of 113 cardiac arrests compared with MCT, most of which should be reversible due to medical

intervention. Still, altering this scenario with more liberal estimates of rehabilitation enrollment and patient exercise would only increase annual cardiac arrest rates by several hundred at most. Similarly, if HIIT causes comparable increases in major cardiac complications to those that have been observed with cardiac arrest rates, anticipated complication rates would be minimal.

The question then becomes, are there enough benefits from adopting HIIT over MCT to justify the safety concerns raised with HIIT? Perhaps the best way to analyzes this question is through examining possible changes in mortality. HIIT offers potential improvements in CVD patient mortality through improvements in VO_2, heart rate recovery and variability, and arterial stiffness. In fact, VO_2 alone can improve mortality by up to 30% per MET increase (Martin et al., 2013). Furthermore, a possibility exists that HIIT could improve mortality through improvements in hypertension, hyperlipidemia, obesity, and diabetes, though these connections still need confirmation. When combined with other benefits besides improvement in mortality, there can be little doubt that the benefits of adopting HIIT exceed the potential risks.

With the conclusion that the benefits of HIIT outweigh the risks, there are several issues cardiac rehabilitation facilities must consider before implementing HIIT. First, including HIIT in cardiac rehabilitation could exacerbate the barriers to participation that patients already face. These traditional barriers to rehabilitation have been thoroughly vetted and include low referral rates, poor physician support, lack of insurance, socioeconomic factors, sociodemographic factors (age, sex, race, or education level etc.), low self-efficiency, problems with transportation, psychosocial barriers, comorbidities, and a view that cardiac rehabilitation is inconvenient (Dunlay et al., 2009). Furthermore, incorporating HIIT could erect other barriers for both staff and patients like low HIIT protocol comprehension, HIIT safety concerns, and beliefs that CVD patients can't tolerate HIIT protocols. Additionally, HIIT integration would potentially add logistical barriers like: maximal

cardiorespiratory fitness tests for HIIT patients (which facilities may not be equipped to preform), additional supervision for patient safety and protocol adherence, offering HIIT specific education, and managing direct and continuing costs of supplying heart rate monitors and employing additional staff. No studies have currently investigated whether these or other unexpected barriers would factor into participation following the inclusion of HIIT. There are research models using the Health-Belief Model or the Socio-Ecological Model, however, that investigators could emulate when developing a HIIT barrier study (Horwood, Williams, and Mandic, 2015; Salihu, Wilson, King, Marty, and Whiteman, 2015).

Factoring in possible logistical challenges with HIIT's proposed benefits leads to the conclusion that HIIT should be integrated into cardiac rehabilitation, with several caveats. Specifically, HIIT shouldn't completely replace MCT but should instead be integrated with MCT in best-fit patients. Selection of ideal patients would include those who have no counter indications to exercise, can be tested with a maximal cardiorespiratory fitness test, have a relatively high functional capacity (8+METs), lack previous modality-limiting musculoskeletal injury, and only with those who express a desire to use the protocol. Even if lower-fitness patients (<8 METs) can tolerate short interval HIIT prescriptions, these protocols should be avoided or used with caution since short interval HIIT has few physiologic benefits over MCT. Furthermore, practitioners should exercise caution when prescribing HIIT to any adult over the age of 65, as studies haven't thoroughly addressed HIIT use in this population (Gomes-Neto et al., 2017).

For those rehabilitation facilities that have the equipment and resources to effectively enact HIIT, this training type offers a potentially beneficial and time efficient protocol for selective patients. HIIT's protocol advantages could result in patients having more time for strength training or education while effectively reducing their mortality risk. There may conceivably be

ramifications in the time requirements for insurance reimbursement if HIIT patients are completing their prescribed exercise more quickly. Rehabilitation centers could effectively accommodate more patients or alleviate time commitments for patients with long commutes. Considering the substantial benefits that HIIT could provide, there should be a concerted effort to incrementally incorporate HIIT prescriptions into cardiac rehabilitation. Though more research on protocol efficacy, barriers, and safety is necessary to facilitate HIIT's integration into cardiac rehabilitation.

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