HIGH INTENSITY INTERVAL TRAINING VERSUS MODERATE INTENSITY CONTINOUS TRAINING ON SOLUBLE ST2 BIOMARKERS IN CHRONIC HEART FAILURE

BY

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CHAPTER I
INTRODUCTION

Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise ***(McDonght et al., 2021).***

Systolic heart failure or heart failure with reduced ejection fraction (HFrEF) is a complex clinical syndrome characterized by structural and/or functional impairment of the left ventricle, resulting in a decrease in heart pump function (left ventricular ejection fraction ≤ 40%), characterized by signs or symptoms of volume overload or manifestations of impaired tissue perfusion (such as dyspnea, edema, fatigue, or impaired exercise tolerance) ***(Bloom et al., 2017).***

The defining characteristic of heart failure with a reduced ejection fraction is decreased systolic function leading to reduced cardiac output and increased filling pressures. To date, no medications that directly enhance systolic function have improved outcomes. Cardiac myosin activators are a new class of myotropes that improve myocardial function by directly augmenting cardiac sarcomere function ***(Psotka and Teerlink 2017).***

It has long been observed that heart failure (HF) is associated with measures of systemic inflammation. In recent years, there have

been significant advancements in the understanding of how inflammation contributes to the pathogenesis and progression of HF. It has long been observed that heart failure (HF) is associated with measures of systemic inflammation. However although numerous studies have validated the association between measures of inflammation and HF severity and prognosis, clinical trials of anti-inflammatory therapies have proven mostly unsuccessful with introduction of new clinical tries of anti-inflammatory therapy discussing its effect on the progression of heart failure ***(Sean et al., 2020).***

ST2 is a member of the Toll-like/interleukin (IL)-1 receptor super family. Due to its cell-signaling capacities, IL-1 plays a central role in the regulation of immune and inflammatory responses and is linked to the processes of infection and inflammation. Through alternative splicing, there are 2 isoforms of ST2: a soluble or serum circulating receptor ST2 (sST2) and a transmembrane receptor ST2 ligand (ST2L) ***(Pascual-Figal and Januzzi 2015).***

The expression of sST2 is largely inducible and almost ubiquitous in living cells, such as resting fibroblasts. It has been suggested that sST2 is produced by both cardiac fibroblasts and cardiomyocytes in response to injury or stress, and by macrovascular (aortic and coronary artery) and heart microvascular endothelial cells in response to diastolic load ***(Ghashghaei et al., 2016).***

Soluble ST2 has been evaluated in a number of clinical cardiovascular diseases CVD studies and is a Food and Drug Administration (FDA) approved prognostic biomarker of mortality in chronic heart failure patients. Previous meta-analyses have shown that sST2 has diagnostic value for heart failure and is prognostic for

all-cause mortality in heart failure, coronary artery disease and following aortic valve replacement. However, there is a paucity of clinical studies on IL-33, which is likely due to difficultly measuring circulating levels ***(Liu et al., 2020)***.

HF patients are often elderly and have many comorbidities, thus they are a challenging population to provide exercise training to. These patients have often been sedentary for a very long time, with a frequent motion-limiting comorbidities. Exercise in heart failure increases the ability to perform sub-maximal activities in daily life, improving quality of life by implementation of different types of exercise ***(Beckers and Gevert 2020).***

Aerobic exercises can be continuous, of moderate intensity or intercalating high and low-intensity efforts. High-intensity interval training (HIIT) is currently one of the most effective methods for improving cardiorespiratory and metabolic function. HIIT involves repeated activities, from short to long ones, of high-intensity exercises combined with periods of active or passive recovery ***(Tschakert and Hofmann 2013)***.

Moderate-intensity continuous training (MICT) is regarded as a successful approach to CR because of its efficacy and safety. Some studies found that MICT can reduce cardiovascular risk and cardiovascular mortality. MICT entails longer durations of moderate-intensity continuous aerobic activity, maintaining intensity between 60 and 80% (VO2peak or reserve heart rate) ***(Yue et al.,2022).***

Recently reported that HIIT is superior to traditional continuous aerobic training in improving cardiac autonomic function and suggested that the effect verified on post-HIIT autonomic

function was related to improve bar reflex modulation and vagal control ***(Kiviniemi et al. 2014).***

Several studies reported exercise-induced Moderate Intensity Continuous Training (MICT) favorable cardiac chambers remodeling in post-infarction and in heart failure (either with reduced or preserved ejection fraction) patients **(Mueller et al., 2021).**

Statement of the Problem:

Is there a significant difference between high intensity interval training versus moderate intensity continuous training on soluble ST2 biomarkers in chronic heart failure?

The Purpose of the Study:

To determine the effect of high intensity interval training versus moderate intensity continuous training on soluble ST2 biomarkers in chronic heart failure.

Significance of the Study:

A recent study of incident HF conducted between 1998 and 2017 in the United Kingdom (UK), age-adjusted rates of first hospitalizations increased by 28% for both all-cause and HF admissions, and by 42% for non-CV admissions. The risk of HF hospitalization is 1.5 times higher in patients with diabetes compared to controls. AF, a higher body mass index (BMI), and higher glycated haemoglobin (HbA1c), as well as a low estimated glomerular filtration rate (eGFR) are strong predictors of HF hospitalizations ***(Lawson et al., 2019).***

Biomarkers have made a significant contribution to the diagnosis and prognosis of disease. Although strongly associated with

inflammatory and autoimmune diseases, ST2 has also been found to play a role in the diagnosis and prognosis of CVD. As one of the isoforms of ST2, sST2 has recently become a promising prognostic indicator for patients diagnosed with HF and a useful tool for risk stratification. Due to its prognostic value, sST2 was recommended by the American College of Cardiology Foundation (ACC)/American Heart Association (AHA) as an important biomarker for monitoring HF patients in 2013 ***(Zhang et al., 2021).***

Several systematic reviews have compared the effectiveness of high intensity interval training (HIIT) and moderate intensity continuous training (MICT) in HF patients. All these studies investigated the changes of VO2peak in HIIT when compared with MICT. However, limited by a few numbers of included studies or a mixture of heart failure in CAD patients, the conclusion was constrained with high heterogeneity. In addition, regarding health outcomes such as other cardiorespiratory parameters, cardiovascular risk factors, left ventricular function and quality of life, there is a lack of investigations and the existing results remain inconsistent ***(Elliott et al., 2015).***

A systematic review and meta-analysis included the latest RCTs aims to evaluate the broad-spectrum physical health benefits of HIIT compared with MICT, with a specific focus on cardiorespiratory fitness, heart rate, blood pressure, blood lipids, left ventricular function and QoL in CAD patients without reduced LVEF or heart failure ***(Xie et al., 2017).***

A comprehensive review of the relevant literature is needed to resolve these limitations and determine the efficacy of HIIT versus MICT in HF patients. This would be helpful to develop a more

targeted and efficient exercise prescription and contribute to more alterative choices in CR management ***(Liou et al., 2016).***

The current study is expected to add important knowledge on the pathophysiology of HF and the clinical benefits of a training intervention as a novel treatment strategy in HF patients, which may help to improve both quality of life (QoL) and functional status in affected patients**.**

Delimitations:

This study will be delimited to the following aspects:

Subjects:

- Sixty male patients with chronic heart failure grade NYHA I, II.
- Patients will be divided into two groups group A receiving HIITS and group B receiving MICT.
- Patients are ready to participate and cooperate actively in our exercise program.
- Patients who will meet one of the following criteria are to be excluded from the study:

1. Signs of acute heart failure, unstable angina or severe arrhythmia three months prior to enrolment in the study.

2. Pacemakers.

3. Chronic obstructive pulmonary disease.

4. Other disorders counteracting exercise testing conditions that limit lower limb mobility (for example, burns, fractures)

5. Pre-existing neuromuscular diseases (for example neuromuscular disorder).

Basic Assumptions:

It will be assumed that:

1. The primary medical assessment will be done to every participating patient which includes:

-Complete medical history (personal, present and past)

- Referral from the physician.

-homodynamic stability without need for vasoactive drugs.

2. All patients will stick to the program and will follow instructions.

3. All other factors which may influence the outcome such as noise and distraction will be controlled.

Hypothesis:

It will be hypothesized that there will be a significant difference between high intensity interval training and moderate intensity

continuous training on soluble ST2 biomarker in patients with chronic heart failure.

CHAPTER II
LITRATURE REVIEW

Heart Failure (HF) is a clinical syndrome characterized of typical symptoms breathlessness, ankle swelling and fatigue that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or exertion ***(Ponikowski et al., 2016)***.

Heart failure is a syndrome characterized initially by left ventricular dysfunction that triggers countermeasures aimed to restore cardiac output. These responses are compensatory at first but eventually become part of the disease process itself leading to further worsening cardiac function ***(Yancy et al., 2016).***

The American College of Cardiology and The American Heart Association ACC/AHA defines Systolic Heart Failure (SHF) as a complex clinical syndrome resulting from any structural or functional cardiac abnormality that impairs the ability of the ventricle to eject blood with manifestations of dyspnea, fatigue, exercise intolerance and fluid retention leading to splanchnic congestion and/or peripheral edema ***(Yancy et al., 2013).***

Similarly, the ESC defines SHF as a clinical symptom characterized by typical symptoms of breathlessness, ankle swelling and fatigue that may be accompanied by signs of elevated jugular pressure, pulmonary crackles and peripheral edema caused by structural and/or functional cardiac abnormality resulting in reduced cardiac output. The two definitions further distinguish SHF from

diastolic heart failure (DHF), the former resulting from impaired contractile function (defined by depressed ventricular ejection < 40%) while the latter results from impaired ventricular filling, compliance or relaxation (defined by a mildly reduced or preserved ejection fraction > 50%) ***(Ponikowski et al., 2016).***

In addition to routine clinical laboratory tests (including natriuretic peptides and cardiac troponins), other biomarkers are gaining attention for their utility in heart failure (HF) management. Among them, soluble ST2 (sST2) a novel biomarker integrating inflammation, fibrosis, and cardiac stress has been included in the 2013 ACCF/AHA guideline for additive risk stratification of patients with acute and chronic HF ***(yancy et al., 2013).***

Soluble ST2 is an interleukin-1 (IL-1) receptor family member, is secreted into the circulation and functions as a "decoy" receptor for IL-33, inhibiting IL-33/ST2 signaling. Blood concentrations of sST2 are increased in various diseases such as inflammatory diseases and heart diseases and are considered a valuable prognostic biomarker in both conditions. Soluble ST2 lacks disease specificity and, therefore, is not a valuable biomarker for the diagnosis of HF**.** In acute and chronic HF, however, sST2 is strongly associated with measures of HF severity and poor outcome. Several studies in patients with HF indicate that serial measurement of sST2 has prognostic value and could have a potential role in future biomarker-directed therapy ***(Dieplinger and Mueller 2015).***

In the issue of Circulation: Heart Failure, ***(Pascual-Figal et al 2018)*** presents the first data indicating the production of soluble ST2 protein by organs other than the heart and vessels. Using an experimental model of HF (permanent left anterior descending

occlusion in a rat model); they measured soluble ST2 mRNA in lung, kidney, and liver tissue samples obtained at prespecified time-points. The liver and kidneys did not participate in ST2 production during any of the studied periods. Concentrations of sST2 have been implicated in the presence and severity of heart failure with particular value for prognostication. It was reviewed the use of sST2 as a prognostic biomarker in heart failure, including present and future directions in this exciting area ***(Bhardwaj and James 2010)***

Much published work has examined and confirmed the beneficial physiological effects of aerobic physical activity or moderate intensity (55%–70% of maximal heart rate (MHR), rate of perceived effort (RPE) of 11–13 on the Borg scale) continuous training, known as MICT. World Health Organization (WHO) recommends a minimum of 150 min per week of aerobic physical activity at moderate continuous intensity to maintain or achieve health ***(Wood et al., 2019).***

Exercise of high submaximal intensity performed in intervals of 1 to 4 minutes, also called high-intensity interval training (HIIT), has been tested in a multiple studies on patients with heart failure with reduced ejection fraction, showing that HIIT was superior to moderate continuous training (MCT) in improving exercise capacity, quality of life, endothelial function, and left ventricular diameter and ejection fraction. The results were better than those observed in previous studies and meta-analyses of patients with chronic heart failure. They also prompted discussions of whether HIIT should be included in standard care of patients with chronic heart failure**.** ***Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2014).***

Despite concerns regarding patient adherence, several studies have shown irrefutable advantages of HIT in patients with cardiac failure. It is interesting that HIT protocols, the total exercise volume, and time commitment have been significantly lower compared to moderate-intensity training, and yet its use still shows various positive physiological benefits that are at least comparable with moderate-intensity protocols. It is also important to note that HIT has been shown to be safe, tolerable, and enjoyable for patients with cardiovascular disease, eliminating any major concerns of an increase in adverse effect risk ***(Hussain et al., 2016).***

CHAPTER III

PATIENTS AND METHODS

The current study is designed to compare the effect of high intensity interval training versus moderate continuous training exercise on soluble ST2 biomarker level in chronic heart failure patients with New York heart association (NYHA) classification I, II.

Patients:

This study will be carried out on sixty male patients suffering from chronic Heart failure NYHA classification (I & II) with an age range from 50 to 60 years old. The patients will be selected from Aldmerdash hospital, Ain shams university and patients will be randomly assigned into two groups. The purpose, nature and potential risk of the study will be explained to all patients.

Ethical considerations:

- Approval of faculty ethical committee.
- The study procedures will be explained for all participants.
- Confidentiality will be assured.
- An informed consent will be taken from each subject prior to participation **(Appendix I).**

Criteria for the patient selection:

Inclusion Criteria:

The patient selection will be according to the following criteria:

- They will have chronic heart failure (New York heart association class I& II) systolic left ventricular dysfunction.
- Their left ventricular ejection fraction (LVEF) <40%.
- Medical treatment will be optimized at least three months prior to study entry.
- All patients didn't participate in any rehabilitation programs prior to the study.

Exclusion criteria:

Patients who will meet one of the following criteria are to be excluded from the study:

- Signs of acute heart failure, unstable angina or severe arrhythmia three months prior to enrolment in the study.
- Pacemakers.

- Chronic obstructive pulmonary disease.
- Other disorders counteracting exercise testing conditions that limit lower limb mobility (for example, burns, fractures)
- Pre-existing neuromuscular diseases (for example Myasthenia Gravis).

Patients will be assigned into two groups with a group A receiving HIIT and group B receiving MICT, both groups will receive their optimal medical treatment.

- All patients will be thoroughly evaluated before and after treatment protocol application.
- All patients will receive their prescribed medical treatment.

Evaluation

Primary outcome to be measured is soluble ST2 biomarker level

Secondary out come to be measured is ejection fraction, quality of life and peak exercise response.

1. Soluble ST2 biomarker

The Presage(®) ST2 Assay

(Critical Diagnostics, CA, USA) is an in vitro diagnostic device that quantitatively measures soluble suppression of tumorigenicity 2 (sST2) in serum and plasma by ELISA ***(Mueller and Dieplinger 2013).***

Procedure: sample will be taken at the cubited vein at the beginning of the program and also at its end.

Echocardiogram. .2

Left ventricular systolic dysfunction will be assessed using the ejection fraction by 2D simpson method (the percentage of the end diastolic volume ejected during systole).

Resting echocardiographic images will be acquired in accordance with American Society of Echocardiography guidelines by a cardiac sonographer, blinded to group allocation ***(Lang et al., 2015).***

Procedure: A commercially available ultrasound system (Vivid S5 or E90, GE Medical Systems, Horten, Norway) equipped with a 2.5-MHz multifrequency phased array transducer will be used to determine the echocardiogram variables by the physician.

3. Minnesota Living with Heart Failure Questionnaire

The questionnaire has 21 items. Assessing the impact of frequent physical symptoms of heart failure. Other items ask about the effects of heart failure on physical and social functions as well as mental and emotional functions. Since treatments might have direct effects on a patient's life in addition to their effects on symptoms and functional limitations of heart failure, questions about side effects of medications, hospital stays and costs of care were included to help measure the overall impact of treatments for heart failure on patients' quality of life.

Procedures: When administering the Minnesota Living with Heart Failure Questionnaire to a subject, the instrument must be

completed fully and it is crucial to explain to the patient why it is important to collect his opinions in order to reduce the number of missing data and therefore maximize the quality of the 10 data collected (Appendix II).

4- Modified Bruce exercise test

A symptom-limited graded treadmill exercise test (GXT) will be carried out prior to the exercise rehabilitation program to tailor the exercise training program using modified Bruce protocol **.**The following exercise parameters will be assessed: a) Exercise duration, b) estimated achieved metabolic equivalent of task (METs), c) basal heart rate (BHR), d) peak heart rate (PHR) and peak exercise response. The exercise test will be repeated after completion of the 3-month CR program to assess the change in functional capacity of the patients with respect to the fore-mentioned parameters ***(Pescatello et al., 2014).***

Procedure:

Exercise will be performed on a treadmill. The leads of the ECG are placed on the chest wall. The treadmill is started at 2.74 km/hr (1.7mph) and at inclinator gradient of 10% after 3 min incline af the treadmill is increased by 2% and the speed increases. The test should be stopped when the subject cannot continue due to fatigue or pain or due to any other medical condition ***(Badawy and Muaidi 2019).***

Training

Management procedures

Group A

Patients will receive medical treatment and will be submitted to the cardiac rehabilitation unit receiving HIIT ***(pelliccia et al., 2021).***

- Frequency: HIIT, MCT will be in 2 supervised sessions per week for 12 weeks on treadmill.
- Intensity: HIIT included 4 minute intervals aiming 60-85% of heart rate reserve separated by 3 min active recovery period of moderate intensity exercise 40-59%of heart rate reserve.
- Duration: The session lasts 30-40 min included warming up and cooling down at moderate intensity**.**

Group B

Patient will receive medical treatment and will be submitted to the cardiac rehabilitation program receiving MICT ***(Mueller et al., 2021).***

- Frequency: Moderate continuous training is scheduled 2 times per week for 12 weeks.
- Intensity: exercise will be applied on treadmill (40%-59% of heart rate reserve)
- Duration: 30-40 minutes per session.

Safety: all the procedures will be applied inside the cardiac rehabilitation unit.

Only the patients who will complete the 3 month CR program attending >80% of the exercise training sessions will be included in this study.

Data analysis:

The collected data will be statistically analyzed using descriptive statistics (the mean and standard deviation).

- The paired t test will be used to determine the significance level between pre and post physical therapy treatment.
- The level of significance < (0.05).

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Appendix I

Sample consent form

I am..... freely and voluntarily consent to participate in this research study under the direction of the researcher Dina Reda Ali Hassan

A thorough description of the procedures has been explained and I understand that I may withdraw my consent and discontinue participation in this research at any time without prejudice to me.

Date: / / 20

Participant/

Appendix II

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little				Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

Note: the questionnaire was taken by personal interviewing