UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effect of HIIT training on endothelial function, heart rate variability and exercise capacity in patients with heart failure

Rowan Smeets

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :
dr. Kenneth VERBOVEN

COPROMOTOR :
Prof. dr. Dominique HANSEN

BEGELEIDER :
Mevrouw Natalia TURRI DA SILVA

UHASSELT
KNOWLEDGE IN ACTION

www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

2020
2021

UHASSELT

KNOWLEDGE IN ACTION

Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The effect of HIIT training on endothelial function, heart rate variability and exercise capacity in patients with heart failure

Rowan Smeets

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :

dr. Kenneth VERBOVEN

BEGELEIDER :

Mevrouw Natalia TURRI DA SILVA

COPROMOTOR :

Prof. dr. Dominique HANSEN

Acknowledgement

For this second part of my thesis, in the second year of the master of Physiotherapy and Rehabilitation Science, I would like to thank the people who have assisted in accomplishing this master thesis.

First, I would like to thank the researchers at the University of Brasilia for the cooperation, the recruitment and testing of participants and sharing of the acquired data.

Furthermore, I want to thank Natália Turri da Silva who supported me as part of her PhD and provided the knowledge and insight in testing required for this thesis.

Finally, I would like to thank Dr. Kenneth Verboven who -as my promotor- assisted the process of writing my thesis. Thank you for the support and for giving me the freedom to research the subject on my own account.

Research context

This master thesis is part of the research domain of rehabilitation of internal disorders. More specifically, this thesis focusses on the rehabilitation of heart failure (HF) patients using high intensity interval training (HIIT).

HF is an increasing health issue with a prevalence that has been (and still is) on the rise. Since the general population is increasing and life expectancy is increasing the prevalence is expected to keep rising (Groenewegen et al., 2020). HF is caused by structural and/or functional abnormality of the heart which in turn reduces the cardiac output and can elevate intracardiac pressures during activities or at rest (Ponikowski et al., 2016). Endothelial function (EF) is vital in the cardiovascular system. Patients with HF have an increased risk of endothelial dysfunction, which may contribute to the progression of HF (Giannitsi et al., 2019). EF assessed through flow-mediated dilation (FMD) is a prognostic factor of mortality and cardiovascular events as well as a predictor of hospitalization through HF progression (Alem, 2019).

Current guidelines for HF rehabilitation include exercise therapy. Exercise therapy has positive effects on general physical function, quality of life and diastolic function (Ponikowski et al., 2016). Exercise has also been proven to increase EF in different populations, including both healthy populations and populations with cardiovascular disease. There was a positive relation between exercise intensity and EF, therefore HIIT may be an effective exercise intervention to improve EF and thus prognosis in HF patients (Ashor et al., 2015).

This is the second part of a master thesis, it is a follow-up of the literature study which studied the effect of HIIT and resistance training on the EF in a HF population. Current available evidence on the effect of HIIT on EF in HF patients is limited and the existing literature is contradictory. The studies by Wisløff et al., (2007) and Munch et al., (2018) support the beneficial effect of HIIT on EF while the studies by Angadi et al., (2015), Benda et al.,(2015) and Thijssen et al., (2019) did not find any effect of HIIT on EF. The goal of this study was to further research the effect of HIIT on EF and other risk factors in HF patients.

This thesis was written during the second master year of Physiotherapy and Rehabilitation Science at the University of Hasselt (academic year 2020-2021). The thesis was part of an international project (University of Hasselt and the University of Brasilia) that investigated the

effects of HIIT and resistance training on EF and physical fitness in patients with HF. . The thesis took place under the supervision of dr. Kenneth Verboven and Prof. dr. Dominique Hansen.

The study design and methods were determined by Rowan Smeets in cooperation with the promotor dr. Kenneth Verboven. Participant recruitment and data acquisition took place in both the University of Hasselt and the University of Brasilia. However due to security concerns over the novel SARS-CoV-2 virus, all activities at the University of Hasselt were shut down promptly. As a consequence all data used in this study were acquired by the University of Brasilia. Data analysis as well as the academic writing were performed by Rowan Smeets.

List of references

Alem, M. M. (2019). Endothelial Dysfunction in Chronic Heart Failure: Assessment, Findings, Significance, and Potential Therapeutic Targets. *International journal of molecular sciences, 20*(13), 3198. doi:10.3390/ijms20133198

Angadi, S. S., Mookadam, F., Lee, C. D., Tucker, W. J., Haykowsky, M. J., & Gaesser, G. A. (2015). High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985), 119*(6), 753-758. doi:10.1152/japplphysiol.00518.2014

Ashor, A. W., Lara, J., Siervo, M., Celis-Morales, C., Oggioni, C., Jakovljevic, D. G., & Mathers, J. C. (2015). Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. *Sports Med, 45*(2), 279-296. doi:10.1007/s40279-014-0272-9

Benda, N. M. M., Seeger, J. P. H., Stevens, G. G. C. F., Hijmans-Kersten, B. T. P., van Dijk, A. P. J., Bellersen, L., . . . Thijssen, D. H. J. (2015). Effects of High-Intensity Interval Training versus Continuous Training on Physical Fitness, Cardiovascular Function and Quality of Life in Heart Failure Patients. *PLoS One, 10*(10), e0141256. doi:10.1371/journal.pone.0141256

Giannitsi, S., Bougiakli, M., Bechlioulis, A., & Naka, K. (2019). Endothelial dysfunction and heart failure: A review of the existing bibliography with emphasis on flow mediated dilation. *JRSM cardiovascular disease, 8*, 2048004019843047-2048004019843047. doi:10.1177/2048004019843047

Groenewegen, A., Rutten, F. H., Mosterd, A., & Hoes, A. W. (2020). Epidemiology of heart failure. *European Journal of Heart Failure, 22*(8), 1342-1356. doi:https://doi.org/10.1002/ejhf.1858

Munch, G. W., Iepsen, U. W., Ryrsø, C. K., Rosenmeier, J. B., Pedersen, B. K., & Mortensen, S. P. (2018). Effect of 6 wk of high-intensity one-legged cycling on functional sympatholysis and ATP signaling in patients with heart failure. *Am J Physiol Heart Circ Physiol, 314*(3), H616-h626. doi:10.1152/ajpheart.00379.2017

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., . . . Group, E. S. D. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal, 37*(27), 2129-2200. doi:10.1093/eurheartj/ehw128

Thijssen, D. H. J., Benda, N. M. M., Kerstens, T. P., Seeger, J. P. H., van Dijk, A. P. J., & Hopman, M. T. E. (2019). 12-Week Exercise Training, Independent of the Type of Exercise, Attenuates Endothelial Ischaemia-Reperfusion Injury in Heart Failure Patients. *Frontiers in physiology, 10*(264). doi:10.3389/fphys.2019.00264

Wisløff, U., Støylen, A., Loennechen, J. P., Bruvold, M., Rognmo, Ø., Haram, P. M., . . . Skjærpe, T. (2007). Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients. *Circulation, 115*(24), 3086-3094. doi:doi:10.1161/CIRCULATIONAHA.106.675041

Table of contents

1 Abstract

Background: Heart failure (HF) prevalence is on the rise and expected to keep rising in the future. Endothelial cells play a vital part in the cardiovascular system. Endothelial dysfunction is often present in HF patients, which may contribute to the progression of HF. Exercise can improve endothelial function (EF) in populations with cardiovascular disease. However which form of exercise is best in improving EF in HF patients is currently unknown.

Objectives: The goal of this paper is to study the effect of high intensity interval training (HIIT) on EF, physical fitness assessed by cardiopulmonary exercise testing (CPET) and heart rate variability (HRV) measurements, in HF patients.

Participants: A total of 17 participants were initially recruited in this randomized controlled trial from HF clinics and local hospital databases by the university of Brasilia. Participants were randomized in an intervention group, receiving 12 weeks of HIIT training with three trainings per week and a control (CT) group, receiving usual care.

Measurements: Participants were subjected to three tests. Flow-mediated dilatation (FMD) was measured to assess EF. A CPET performed on a stationary bicycle was used to determine endurance capacity and an appropriate exercise intensity during the intervention. Other outcomes from the CPET included absolute/relative VO2peak and peak power. HRV measurements were performed which are related to prognosis in HF patients. All measurements were performed at baseline and after a 12 week follow up.

Results: The HIIT group significantly increased in relative VO2peak and absolute peak power by 12% and 18%, respectively. There were no significant changes in FMD or HRV outcomes within groups. Neither were there differences between group effects of FMD or HRV at post intervention measurements.

Conclusion: Twelve weeks of HIIT training can improve physical fitness in HF patients. No effects of HIIT on EF or HRV were found. Findings of this study were limited due to the small sample size.

Keywords: High intensity interval training, Endothelial function, Flow-mediated dilatation, Heart rate variability, Hemodynamic monitoring, Cardiopulmonary exercise test, Oxygen uptake

2 Introduction

Heart failure (HF) is a clinical syndrome caused by a structural and/or functional defect of the heart, resulting in impairment of cardiac output and/or intracardiac pressures during stress or at rest. Symptoms present in these patients depend on the pathophysiology and often include breathlessness at rest or during physical activity, pulmonary or peripheral edema, and fatigue. Other signs include an elevated venous pressure or pulmonary crackles (Ponikowski et al., 2016).

The diagnosis of HF is based on echocardiography, which objectifies the ventricular function, amongst other variables. Based on the echocardiography, patients are classified according to their respective left ventricular ejection fraction (LVEF). Three classes can be distinguished: patients with reduced LVEF (<40%) are classified as HF with “reduced” ejection fraction (HFrEF), patients with no reduction in LVEF (≥50%) are classified as HF with “preserved” ejection fraction (HFpEF). Patients with a LVEF between the mentioned values are classified as HF with “mid-range” ejection fraction (HFmEF) (Ponikowski et al., 2016). Alternatively, HF patients can be classified based on the severity of their symptoms, using the New York heart association (NYHA) classification. This system consists of four gradual, conditional classes that take both symptoms and exercise (in)tolerance into account. Only one class can be assigned to an individual at one time. Though, over time, their class may change (Ponikowski et al., 2016). The NYHA classification is commonly used to classify patients, however, to obtain detailed insights in the cardiac and pulmonary function and exercise (in)tolerance the cardiopulmonary exercise test (CPET) is used (Malhotra et al., 2016; Guazzi et al., 2017).

According to Dunlay et al., (2014) the current prevalence of HF in the USA and Europe ranges from 1% to 14%, and despite the increasing knowledge about HF, the overall prognosis remains poor. The mortality rates for acutely hospitalized HF patients range from 5.8% to 8.1%, while the 5-year mortality rate for diagnosed HF patients is 43% (Guha et al., 2013; Hobbs et al., 2007; Nieminen et al., 2006; Nicol et al., 2008). The prognosis of HF can be based on different risk predictors including the NYHA classification, LVEF or heart rate variability (HRV) (Bredy et al.,2018; Di Tanna et al., 2020; Nolan et al., 1998). HRV is evaluated by comparing variability in the intervals between heartbeats (demonstrated as R waves). A healthy heart also has time differences between heartbeats, therefore an evaluation over a

period of time is applied. In patients with HF, an overall lower standard deviation in intervals between normal R waves is linked with an increased risk of mortality due to progressive HF and a higher all-cause mortality. (Shaffer et al.,2017; Boveda et al.,2001; Camm et al., 1996; Nolan et al.,1998)

Increasing severity of HF status may occur as a result of numerous factors. One of those factors is a decline in endothelial function (EF). Endothelial cells (EC), forming the inner surface of blood vessels, play a key role in regulating blood flow by releasing nitric oxide (NO) causing vasodilation. A decreased function of the endothelium causes an altered reaction to physiological stimuli, e.g. an inappropriate vascular response to physical activity. When coronary vasodilation is decreased, impaired myocardial perfusion occurs, resulting in an impaired ventricular function (Colombo et al., 2008; Giannitsi et al., 2019). Furthermore, the release of NO by the EC regulates the redistribution of blood flow during exercise. This process leads to an impaired exercise capacity in HF patients (Giannitsi et al., 2019). In practice, EF can be assessed through various means: assessing biomarker levels in the blood or invasively infusing vasoactive compounds and observing the response. Alternatively, there are non-invasive options such as venous occlusion digital plethysmography, brachial artery flow-mediated dilation (FMD) and peripheral artery tonometry (Giannitsi et al., 2019).

Research has shown that exercise is an effective treatment to improve EF in various populations, among which coronary artery disease and HF populations (Ashor et al., 2015; Ramos et al., 2015). Current guidelines for HF strongly recommend regular aerobic exercise, as exercise improves health-related quality of life and HF hospitalization rates (Ponikowski et al., 2016). Compared to continuous aerobic exercise HIIT is more effective and more time efficient in increasing exercise capacity. HIIT training consists out of short bouts of high intensity work (90-95% peak exercise capacity) alternated with recovery periods (Piepoli et al., 2011). In terms of EF, higher exercise intensities induce more shear stress in the endothelium, which tends to have beneficial effects on EF (Ashor et al., 2015). HIIT has the potential to elicit high shear stress and may therefore have a beneficial effect on EF.

The goal of this study is to explore the effects of HIIT on EF, physical fitness and HRV, in patients with HF.

3 Methods

3.1 Design

This study is a randomized controlled trial conducted by the university of Hasselt in cooperation with the university of Brasilia. Recruiting started in February 2020 at the university of Hasselt . However, due to safety precautions concerning the novel SARS-CoV-2 virus, all recruitments, thus tests and interventions were ceased at the university of Hasselt. A total of 17 patients were previously (2019) recruited and randomized by the university of Brasilia. The trial was approved by the University of Brasilia (Brasilia, Brazil) (registration number RBR-668c8v) and was performed in accordance with the standards set by the latest revision (2013) of the Declaration of Helsinki. A written informed consent was obtained from all participants included in the trial.

3.2 Participants

Local hospital databases and HF clinics were contacted for the recruitment of participants. Patients were eligible if they had HF diagnosed by means of echocardiography and were considered “clinically stable” by their cardiologist. Patients with muscle injuries, joint injuries or orthopedic conditions that would intervene with compliance to the intervention were excluded. Other exclusion criteria were: respiratory restrictions (FEV1<50%), any inflammatory conditions, Chagas disease, smoking, recent participation in training programs (<6 months before recruitment) or pregnancy (or planned pregnancy while participating).

A total of 17 participants were recruited and randomized in the high intensity interval training (HIIT) group or control (CT) group. Subjects were randomized after baseline measurements using a random sequence generator. Randomization was stratified according to age and HF classification based on LVEF to ensure comparable baseline characteristics. Sealed envelopes were used to ensure blinding of randomization of the participants in either the HIIT group or CT group. Tables 1 provides a complete list of baseline characteristics of all included subjects.

3.3 Procedure

3.3.1 Intervention

Patients in the HIIT group were subjected to a 12-week supervised training program consisting of 3 weekly HIIT sessions. The intensity of the intervals was based on the results of a baseline CPET. Each training session consisted of four intervals of three minutes each at an intensity 10% above the second ventilatory threshold (VT2), alternated with four minutes of recovery at an intensity 10% above the first ventilatory threshold (VT1). (Wisløff et al., 2007; Piepoli et al., 2011). Each session was preceded by a short warming up period (10 min). The first 6 sessions of the training program were used to allow subjects to adapt to the training protocol. In these first sessions subjects performed a moderate intense continuous aerobic training for 30 minutes, intensity was gradually increased starting at an intensity slightly above VT1. Subjects would switch between running/walking on a treadmill and cycling on a stationary bicycle. Alternation between those two options was provided to prevent overuse injuries.
Training intensity was monitored by heart rate (HR). As a safety precaution several physiological variables (i.e., HR, blood pressure and Borg rate of perceived exertion) were monitored before and after each training session (data not shown in the current paper).
Patients in the CT group did not participate in any training program and were instructed to maintain their usual activity level.

3.3.2 Measurements

Upon entering the study, participants were subjected to the following measurements: FMD, CPET and HRV over a period of 30 minutes. Participants were asked not to consume caffeine or alcohol within 24 hours prior to the tests, as well as not to participate in sports or training within the same timeframe. On a day of testing, participants were allowed a small meal which should have preceded the tests by at least two hours.

For the FMD measurement, a Doppler duplex ultrasound machine (HD11.XZ, 1 and 3 MHZ, Phillips), with a linear array, was used in order to assess the arterial blood flow and artery diameter simultaneously. All variables were analysed using FMD studio (Version 4.2.0, Cardiovascular Suite, Qiupu, Pisa, Italy). The post intervention test was planned at the same time of the day as the initial test to avoid influences regarding circadian rhythm. The room temperature when testing FMD was regulated and kept at ~24°C. Participants were positioned

supine with the arm in a relaxed position. First, the patient is given five minutes in the supine position in order to stabilize blood pressure and other cardiovascular reactions. A cuff is placed around the arm below the antecubital fossa and the linear probe (9Mhz) is used to search for a clear image of the brachial artery approximately 10 centimeters proximal to the cuff. Both arterial diameter and blood flow were measured using duplex ultrasound (duplex mode; pulse frequency 5MHz; angular correction 60°). A baseline measure was recorded for two minutes. Then the cuff was inflated to a pressure of 220 mmHg in order to occlude the blood flow for five minutes. After five minutes, the cuff was rapidly deflated and the recording was continued for three more minutes. The primary outcome for FMD was acquired by comparing the change in baseline arterial diameter with the post deflating arterial diameter and was expressed in percentage. A reduction in FMD is related to a reduced endothelial function (Giannitsi et al., 2019). A more detailed explanation of the used protocol is described in a study by Leryn et al., (2013).

The results of the FMD test for evaluation of the EF was accessible for nine of the 17 participants. Data of three participants in the HIIT group and five participants in the CT group was lost due to technical problems with the recording.

The CPET was conducted on a stationary bicycle (Corival, LODE BV Medical Technology Groningen - Netherlands). During the test participants were continually monitored using a 12-lead ECG. Oxygen intake and carbon dioxide output were analysed using a “breath-by-breath” ergo-spirometry system (Cosmed, Rome, Italy). A short warm-up period preceded the test. Participants were instructed to keep the rotations per minute (RPM) of the stationary bicycle between 65-80 RPM. The starting workload was set at either 20 Watt or 25 Watt and was increased every minute by 20 Watt until failure to meet the required RPM or until the participant stopped due to fatigue. All participants received verbal encouragement to keep going for as long as possible. Peak effort was assessed through inquiry of fatigue and confirmed when respiratory exchange rate (RER) was ≥1.10. The training intensities used by the HIIT group were based on the results of the initial CPET. The outcomes acquired from the CPET include peak oxygen uptake (VO2peak), VO2peak relative to TBW (VO2peak TBW), Peak power output (Pmax), RER and minute ventilation over carbon dioxide production slope (VE/VCO2 slope). VO2 peak and VE/VCO2 slope are factors related to prognosis in HF patients (Nadruz et al., 2017). All participants in this study completed the CPET at baseline and after

12 weeks. Data for the VE/VCO2 slope at baseline was lost in two participants allocated to the HIIT group. Missing data was not included in the statistical analysis.

HRV is evaluated by measuring time between R-waves using a Polar RS8000 (Polar Electro®, Finland) heart rate monitor. Only the intervals between normal QRS complexes were evaluated. Analysis of HRV was done using specialized software (Kubios HRV version 3.4.3 for Windows). During this test the subject was asked to remain in a supine position for 30 minutes and maintain a normal breathing pattern, while staying awake. During this time the heart rate monitor records continuously. Data provided by the heart rate monitor was later analysed using the specialized software. The HRV of the participants was monitored for 30 minutes, which offered, according to a study by Voss et al., (2013), comparable risk stratification with a 24-hour analysis.

The primary outcome was SDNN, which is the standard deviation of the so called normal-to-normal intervals (NN). Other outcomes included: the square root of the mean squared differences of successive NN intervals (RMSSD), and the HRV triangular index (Hrtri). SDNN is considered the square root of variance between heartbeats, able to give insight to the cyclic components which cause variability within the recording timeframe (Camm et al., 1996). Rrtri was calculated by dividing the integral of the density of the RR interval histogram by the height of the same histogram. SDNN, RMSSD and Rrtri are all considered to be of prognostic value, patients with decreased HRV measures were at a higher risk of death due to progressive HF and all-cause mortality (Camm et al., 1996; Boveda et al., 2001). Data was lost for two participants of the HIIT group due to technical problems during the measurement. All measurements were conducted by the same researcher to avoid inter-rater variability. The researcher was not blinded for group allocation.

3.4 Data analysis

The software JMP® Pro, Version 15.2.0 (SAS Institute Inc., Cary, NC, 1989-2019) was used to analyse the data. The responses of the FMD measurement, CPET and HRV measurements all consisted of continuous data. The covariate in this study was group allocation which is a categorical covariate. The goal of data analysis in this study was to compare the means both between the two groups and within groups.

Before statistical tests could be performed, a normal distribution (tested with the Shaprio-Wilk test), equality of variance (tested with the Brown-Forsythe test) and independency were evaluated. When all assumptions were met, a parametric test could be used, which was the case for between group testing and comparing within group means, using an independent student T-test and a paired student T-test respectively. If one of these assumptions was not fulfilled a non-parametric test was performed. Therefore, comparing between group means was tested with the Wilcoxon's rank sum test, while a Wilcoxon signed rank test was used for comparing within group means.

Differences in baseline may affect the power of this study. To adjust for possible differences in baseline variables, the main outcomes of this study were subjected to a second analysis. An analysis of covariance (ANCOVA) was used to adjust for possible baseline differences in the subjects in the following outcome measures: VO2peak relative to TBW, absolute VO2peak, VE/VCO2 slope and RMSSD. The outcome measures for FMD, SDNN and Rrtri did not have a linear relation between baseline measurement and post-intervention measurement. An ANCOVA would not increase power for these outcomes, instead a repeated measures analysis of variance (ANOVA) was used to test for interactions between group allocation and time of measurement.

In the baseline characteristics both categorical and continue responses were present. For the continue responses the same steps were taken as in the between group analysis for the outcome measures. The categorical data was analysed using Fisher's exact test as sample sizes were too small to use a Chi-squared test.

A statistical test was considered significant if the alfa level was lower than 0.05.

4 Results

4.1 FMD

No between group differences were found at either baseline or post intervention for either FMD or in patients' characteristics (table1). Neither the CT group, nor the HIIT group had significant within group differences between baseline and post intervention testing (Table 2). Analysis with repeated measures ANOVA revealed there were no effects of either group or time of measurement on the outcome of FMD. Furthermore there was no interaction between group and time of FMD measurement, meaning there was no difference in change over time between the two groups (Table 3).

FMD did not correlate to any of the other main outcomes or to LVEF (table 4).

4.2 CPET

All 17 participants completed a CPET at the start of the study and after 12 weeks. There were no significant between group differences at baseline in outcomes of the CPET.

After the 12 week training period patients enrolled in the HIIT showed an improvement in Pmax of 18% ($P<0.01$; Table 5). The HIIT group also showed improvement in VO2peak TBW by 12% ($p<0.05$; Table 5). Also within the HIIT group, the change in absolute VO2peak failed to reach significance ($p=0.09$). The VE/VCO2 slope did not change significantly in the intervention group ($p=0.22$). Within the CT group there was a significant increase in VE/VCO2 slope ($P<0.01$), other CPET outcomes did not change significantly within the CT group. Although there were significant within group changes there were no significant differences between groups at either baseline or after the intervention (Table 5).

When adjusted for baseline differences using ANCOVA it revealed that participants of the HIIT group had significantly more improvement in VO2peak TBW over the CT group ($p<0.05$). The change in VE/VCO2 slope however was not significantly different between groups when adjusted for baseline measurements ($p=0.50$). There was a significant relation between baseline measurements of VO2peak TBW, VO2peak and VE/VCO2 slope and the post intervention measurements (Table 6).

CPET outcomes had no significant correlations to other main outcomes or LVEF (table 4).

4.3 HRV

There was a significant difference between groups at baseline for SDNN ($P<0.05$, RMSSD ($P<0.05$) and Rrtri ($P<0.01$). The CT group showed a lower HRV which is related to poor prognosis in HF patients (Camm et al., 1996; Boveda et al., 2001). The differences between groups remained significant post intervention (Table 7). No between group difference was found for the mean RR intervals (ms) at either pre or post intervention. No within group differences were found for any of the outcome measures (Table 7)

When corrected for baseline differences using ANCOVA there was no significant effect of the intervention on RMSSD compared to the CT group. Similarly a repeated measures ANOVA revealed no interactions between group allocation and time of measurement in outcomes for SDNN and Rrtri (Table 3). This means that there were no significant intervention effects in HRV between either group on HRV outcomes. ANOVA confirmed the between group differences in baseline measurements at pre and post intervention measurements.

There was a correlation between higher ejection fraction to a worse baseline RMSSD ($r=-0.54$; $P=0.001$; table 4). Other HRV outcomes did not have any significant correlation with ejection fraction. No significant correlation between HRV outcomes and other main outcomes were found.

5 Discussion

The aim of the present study was to examine the effect of HIIT on EF and the effect on risk factors in a HF population. The hypothesis stated that HIIT has a positive effect on EF, physical fitness and HRV in patients with HF.

The main finding of this study was that the intervention had a positive effect on VO2peak TBW ($p<0.05$). Although, changes in absolute VO2peak failed to reach significance ($p=0.09$). The CT group appeared to have a significant rise in VE/VCO2 slope ($p<0.01$), which is related to an increased risk of hospitalization (Nadruz et al.,2017). Analysis with adjustment for baseline differences revealed no group effects on VE/VCO2 slope ($p=0.50$) The intervention group did not show statistically significant changes in VE/VCO2 slope nor were there between group differences at either pre or post intervention testing.

Previous research has established that HIIT has a positive effect on VO2peak in HF patients (Ballesta García et al., 2019). The results of the present study failed to comply to those findings. There was however an improvement in VO2peak TBW and Pmax which suggested an increase in exercise capacity. It is possible that sample size was not large enough to detect a change in VO2peak within the intervention group. Overall the risk factors VO2 peak and VE/VCO2 did not differ between groups when corrected for baseline differences.

This study failed to find an effect of HIIT on EF using FMD measurements. No significant change in FMD was detected in either the HIIT group or the CT group. FMD measurement is considered the gold standard for non-invasive assessment of endothelial function (Stoner et al., 2012). However FMD measurements also have a caveat. The accuracy of the FMD measurement is dependent on the skill and experience of the researcher. Therefore it is important to have an experienced researcher who regularly practises the technique to assure good measurements (Corretti et al., 2002). In order to decrease interobserver variability the same researcher conducted both the pre and post intervention test in this study.

The number of studies on the effect of HIIT on EF in a HF population is limited and results of these studies are conflicting. Several studies find a positive effect of HIIT on EF, while other studies fail to find any significant effects (Angadi et al., 2015; Benda et al., 2015a; Munch et al., 2018; Thijssen et al., 2019; Wisløff et al., 2007). The mean and standard deviation of FMD found in this study was similar to that of comparable studies (Angadi et al.,2015; Benda et al., 2015a; Thijssen et al., 2019). None of these studies could detect a difference in endothelial

function measured by FMD as a result of HIIT. However the FMD means in these studies and the FMD measurements in this study did not differ from that of a normal population (Skaug et al., 2013) . Considering there is no noticeable decrease in EF in our sample the improvements due to the intervention could be too minimal to be found significant.

A meta-analysis by Ramos et al., (2015) on the effect of HIIT on EF found HIIT to be an effective exercise form to improve EF. However, the population of this meta-analysis was not limited to HF patients. As for now it is still unclear whether HIIT has the potential to positively affect EF in HF patients.

It is possible that HIIT is less effective at increasing EF in HF patients compared to a healthy population. A possible explanation for this is a less beneficial pattern in shear rate of HF patients during exercise, this was evaluated by Benda et al., (2015b) who measured the oscillatory shear index of HF patients while cycling at moderate intensity and compared it to healthy subjects. However it is unclear whether this shear rate pattern is unfavourable in other exercise modalities such as running/walking. It is also unclear if the shear rate pattern remains unfavourable when cycling at higher intensities.

This study used both cycling and walking as an intervention, it is possible that one of these is superior to the other, however no research to compare these modalities was found. The studies by Wisløff et al., (2007) and Munch et al., (2018) used only walking as exercise intervention. Both these studies found significant effects of HIIT on EF in participants with HF.

For HRV, three main outcomes were related to mortality due to progressive HF, namely SDNN, RMSSD and Rrtri (Camm et al., 1996; Boveda et al., 2001). A fourth main HRV outcome related to higher risk is SDANN, which is the standard deviation of the average NN intervals for each 5 minutes period of a 24-hour recording. SDANN was not included because the recordings in the present study were done over a timeframe of only 30 minutes. Previous research on the effect of exercise training on HRV found exercise to have a positive effect on the RMSSD (Pearson & Smart, 2017). There is however no consensus yet on appropriate exercise intensity, duration or frequency.

There was a significant difference in baseline HRV outcomes between the two groups. For SDNN, RMSSD and Rrtri the baseline measurement was significantly lower in the CT group.

The baseline measures of SDNN, RMSSD and Rrtri of the intervention group were compared and considered within the normal range of HRV (Nunan et al., 2010). The higher baseline

values in the intervention group could be a possible explanation for not finding differences within the intervention group.
It should be noted that the duration of the HRV measurement in this study was 30 minutes which is considered as a short term measurement. Caution should be taken when comparing HRV measurements of different duration as there are changing variances between different recording durations (Camm et al., 1996).

One of the strengths of this study was the personal guidance participants received during training. Every participant had a one-on-one supervision by a physiotherapist. This helped to ensure adherence to the training protocol and appropriate training intensity. It also ensured that every patient completed the required weekly training frequency. Supervision of training in HF patients is advised as it allows for better education and control of adherence, it also offers reassurance for the participant (Piepoli et al., 2011). Supervision also allows for monitoring of physiological responses such as HR, blood pressure and Borg rate of perceived exertion which are recommended during HIIT in order to ensure the safety of the patient (Wewege et al., 2018).

A limitation of the present study was the small sample size, which could be a possible cause of shortage of statistical power to detect significance in the outcome measures. Furthermore, the data of eight participants was lost due to technical problems in the recording of FMD measurements. This severely limited the useable data for analysis further impairing the power of the study. HRV could not be acquired for two participants due to technical difficulties during measurements. Furthermore the VE/VCO2 slope for two participants of the HIIT group could not be calculated for the baseline measurement. The amount of missing data in this study raises concern for the reliability of the reported data for this study. Although data was missing for several outcomes due to technical difficulties there were no dropouts during this study. All participants in the HIIT program completed the entire intervention program with three sessions per week for a duration of 12 weeks. There were no adverse effects due to the intervention. Another limitation of the study was failing to blind the outcome assessors for group allocations. Blinding of the participants and therapists supervising training was not possible due to the nature of the intervention.

A recommendation for future research include striving for a larger sample size to improve statistical power. Also using a trained assessor for FMD measurement, as well as for HRV is recommended to standardize the measurement to ensure comparability to previous and future studies. Future researchers should also take note of the possibility of technical difficulties and should ensure planning of the study allows for additional retesting to avoid missing data.

6 Conclusion

The current study showed that 12 weeks of HIIT improved exercise capacity of HF patients represented by an improved Pmax and an improved relative VO2peak . HIIT training did not improve EF in HF patients and no improvements on risk factors of HRV were found. Overall 12 weeks of HIIT did not affect EF and HRV in HF patients. However the power of this study is limited due to its small sample size and further research with a larger sample size is recommended.

7 List of references

Angadi, S. S., Mookadam, F., Lee, C. D., Tucker, W. J., Haykowsky, M. J., & Gaesser, G. A. (2015). High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: a pilot study. *J Appl Physiol (1985), 119*(6), 753-758. doi:10.1152/japplphysiol.00518.2014

Ashor, A. W., Lara, J., Siervo, M., Celis-Morales, C., Oggioni, C., Jakovljevic, D. G., & Mathers, J. C. (2015). Exercise modalities and endothelial function: a systematic review and dose-response meta-analysis of randomized controlled trials. *Sports Med, 45*(2), 279-296. doi:10.1007/s40279-014-0272-9

Ballesta García, I., Rubio Arias, J., Ramos Campo, D. J., Martínez González-Moro, I., & Carrasco Poyatos, M. (2019). High-intensity Interval Training Dosage for Heart Failure and Coronary Artery Disease Cardiac Rehabilitation. A Systematic Review and Meta-analysis. *Rev Esp Cardiol (Engl Ed), 72*(3), 233-243. doi:10.1016/j.rec.2018.02.015

Benda, N. M. M., Seeger, J. P. H., Stevens, G. G. C. F., Hijmans-Kersten, B. T. P., van Dijk, A. P. J., Bellersen, L., . . . Thijssen, D. H. J. (2015). Effects of High-Intensity Interval Training versus Continuous Training on Physical Fitness, Cardiovascular Function and Quality of Life in Heart Failure Patients. *PLoS One, 10*(10), e0141256. doi:10.1371/journal.pone.0141256

Benda, N. M. M., Seeger, J. P. H., van Lier, D. P. T., Bellersen, L., van Dijk, A. P. J., Hopman, M. T. E., & Thijssen, D. H. J. (2015). Heart failure patients demonstrate impaired changes in brachial artery blood flow and shear rate pattern during moderate-intensity cycle exercise. *Experimental physiology, 100*(4), 463-474. doi:10.1113/ep085040

Boveda, S., Galinier, M., Pathak, A., Fourcade, J. l., Dongay, B., Benchendikh, D., . . . Bounhoure, J.-P. (2001). Prognostic Value of Heart Rate Variability in Time Domain Analysis in Congestive Heart Failure. *Journal of Interventional Cardiac Electrophysiology, 5*(2), 181-187. doi:10.1023/A:1011485609838

Boyle, L. J., Credeur, D. P., Jenkins, N. T., Padilla, J., Leidy, H. J., Thyfault, J. P., & Fadel, P. J. (2013). Impact of reduced daily physical activity on conduit artery flow-mediated dilation and circulating endothelial microparticles. *Journal of Applied Physiology, 115*(10), 1519-1525. doi:10.1152/japplphysiol.00837.2013

Bredy, C., Ministeri, M., Kempny, A., Alonso-Gonzalez, R., Swan, L., Uebing, A., . . . Dimopoulos, K. (2018). New York Heart Association (NYHA) classification in adults with congenital heart disease: relation to objective measures of exercise and outcome. *Eur Heart J Qual Care Clin Outcomes, 4*(1), 51-58. doi:10.1093/ehjqcco/qcx031

Colombo, P. C., Onat, D., & Sabbah, H. N. (2008). Acute heart failure as "acute endothelitis"--Interaction of fluid overload and endothelial dysfunction. *Eur J Heart Fail, 10*(2), 170-175. doi:10.1016/j.ejheart.2007.12.007

Corretti, M. C., Anderson, T. J., Benjamin, E. J., Celermajer, D., Charbonneau, F., Creager, M. A., . . . Vogel, R. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. *Journal of the American College of Cardiology, 39*(2), 257-265. doi:https://doi.org/10.1016/S0735-1097(01)01746-6

Di Tanna, G. L., Wirtz, H., Burrows, K. L., & Globe, G. (2020). Evaluating risk prediction models for adults with heart failure: A systematic literature review. *PLoS One, 15*(1), e0224135. doi:10.1371/journal.pone.0224135

Dunlay, S. M., & Roger, V. L. (2014). Understanding the epidemic of heart failure: past, present, and future. *Curr Heart Fail Rep, 11*(4), 404-415. doi:10.1007/s11897-014-0220-x

Electrophysiology, T. F. o. t. E. S. o. C. t. N. A. S. o. P. (1996). Heart Rate Variability. *Circulation, 93*(5), 1043-1065. doi:doi:10.1161/01.CIR.93.5.1043

Giannitsi, S., Bougiakli, M., Bechlioulis, A., & Naka, K. (2019). Endothelial dysfunction and heart failure: A review of the existing bibliography with emphasis on flow mediated dilation. *JRSM cardiovascular disease, 8*, 2048004019843047-2048004019843047. doi:10.1177/2048004019843047

Guazzi, M., Bandera, F., Ozemek, C., Systrom, D., & Arena, R. (2017). Cardiopulmonary Exercise Testing: What Is its Value? *Journal of the American College of Cardiology, 70*(13), 1618-1636. doi:https://doi.org/10.1016/j.jacc.2017.08.012

Guha, K., & McDonagh, T. (2013). Heart failure epidemiology: European perspective. *Curr Cardiol Rev, 9*(2), 123-127. doi:10.2174/1573403x11309020005

Hobbs, F. D., Roalfe, A. K., Davis, R. C., Davies, M. K., & Hare, R. (2007). Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). *Eur Heart J, 28*(9), 1128-1134. doi:10.1093/eurheartj/ehm102

Malhotra, R., Bakken, K., D'Elia, E., & Lewis, G. D. (2016). Cardiopulmonary Exercise Testing in Heart Failure. *JACC: Heart Failure, 4*(8), 607-616. doi:https://doi.org/10.1016/j.jchf.2016.03.022

Munch, G. W., Iepsen, U. W., Ryrsø, C. K., Rosenmeier, J. B., Pedersen, B. K., & Mortensen, S. P. (2018). Effect of 6 wk of high-intensity one-legged cycling on functional sympatholysis and ATP signaling in patients with heart failure. *Am J Physiol Heart Circ Physiol, 314*(3), H616-h626. doi:10.1152/ajpheart.00379.2017

Nadruz, W., Jr., West, E., Sengeløv, M., Santos, M., Groarke, J. D., Forman, D. E., . . . Shah, A. M. (2017). Prognostic Value of Cardiopulmonary Exercise Testing in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction. *J Am Heart Assoc, 6*(11). doi:10.1161/jaha.117.006000

Nicol, E. D., Fittall, B., Roughton, M., Cleland, J. G., Dargie, H., & Cowie, M. R. (2008). NHS heart failure survey: a survey of acute heart failure admissions in England, Wales and Northern Ireland. *Heart, 94*(2), 172-177. doi:10.1136/hrt.2007.124107

Nieminen, M. S., Brutsaert, D., Dickstein, K., Drexler, H., Follath, F., Harjola, V. P., . . . Tavazzi, L. (2006). EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J, 27*(22), 2725-2736. doi:10.1093/eurheartj/ehl193

Nolan, J., Batin, P. D., Andrews, R., Lindsay, S. J., Brooksby, P., Mullen, M., . . . Fox, K. A. A. (1998). Prospective Study of Heart Rate Variability and Mortality in Chronic Heart Failure. *Circulation, 98*(15), 1510-1516. doi:doi:10.1161/01.CIR.98.15.1510

Nunan, D., Sandercock, G. R., & Brodie, D. A. (2010). A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. *Pacing Clin Electrophysiol, 33*(11), 1407-1417. doi:10.1111/j.1540-8159.2010.02841.x

Pearson, M. J., & Smart, N. A. (2018). Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis. *Heart Fail Rev, 23*(1), 91-108. doi:10.1007/s10741-017-9662-z

Piepoli, M. F., Conraads, V., Corrà, U., Dickstein, K., Francis, D. P., Jaarsma, T., . . . Ponikowski, P. P. (2011). Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Heart Failure, 13*(4), 347-357. doi:https://doi.org/10.1093/eurjhf/hfr017

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., . . . Group, E. S. D. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal, 37*(27), 2129-2200. doi:10.1093/eurheartj/ehw128

Ramos, J. S., Dalleck, L. C., Tjonna, A. E., Beetham, K. S., & Coombes, J. S. (2015). The Impact of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training on Vascular Function: a Systematic Review and Meta-Analysis. *Sports Medicine, 45*(5), 679-692. doi:10.1007/s40279-015-0321-z

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health, 5*, 258. doi:10.3389/fpubh.2017.00258

Skaug, E. A., Aspenes, S. T., Oldervoll, L., Mørkedal, B., Vatten, L., Wisløff, U., & Ellingsen, O. (2013). Age and gender differences of endothelial function in 4739 healthy adults: the HUNT3 Fitness Study. *Eur J Prev Cardiol, 20*(4), 531-540. doi:10.1177/2047487312444234

Stoner, L., Tarrant, M. A., Fryer, S., & Faulkner, J. (2013). How should flow-mediated dilation be normalized to its stimulus? *Clin Physiol Funct Imaging, 33*(1), 75-78. doi:10.1111/j.1475-097X.2012.01154.x

Thijssen, D. H. J., Benda, N. M. M., Kerstens, T. P., Seeger, J. P. H., van Dijk, A. P. J., & Hopman, M. T. E. (2019). 12-Week Exercise Training, Independent of the Type of Exercise, Attenuates Endothelial Ischaemia-Reperfusion Injury in Heart Failure Patients. *Frontiers in physiology, 10*(264). doi:10.3389/fphys.2019.00264

Voss, A., Schroeder, R., Vallverdú, M., Schulz, S., Cygankiewicz, I., Vázquez, R., . . . Caminal, P. (2013). Short-term vs. long-term heart rate variability in ischemic cardiomyopathy risk stratification. *Front Physiol, 4*, 364. doi:10.3389/fphys.2013.00364

Wewege Michael, A., Ahn, D., Yu, J., Liou, K., & Keech, A. (2018). High-Intensity Interval Training for Patients With Cardiovascular Disease—Is It Safe? A Systematic Review. *Journal of the American Heart Association, 7*(21), e009305. doi:10.1161/JAHA.118.009305

Wisløff, U., Støylen, A., Loennechen, J. P., Bruvold, M., Rognmo, Ø., Haram, P. M., . . . Skjærpe, T. (2007). Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients. *Circulation, 115*(24), 3086-3094. doi:doi:10.1161/CIRCULATIONAHA.106.675041

8 Appendix

Table 1: Baseline characteristics and medication

Table 2: FMD measurements

Table 3: Across group effects

Table 4: Correlations between main outcomes at baseline

Table 5: CPET

Table 6: Adjustment for baseline

Table 7: HRV measurements

Table 1

Baseline characteristics and medication

	HIIT (N=8)	CT (N=9)	P value
Age	61 ± 10	54. ± 11	0.20
LVEF%	50.38 ± 17.03	47.20 ± 13.49	0.67
BMI	29.40 ± 5.23	28.30 ± 4.33	0.64
VO2peak (ml/kg/min)	17.48 ± 4.22	21.07 ± 4.13	0.10
Gender (M/F)	5/3	8/1	0.29
NYHA (I/II/III/VI)	3/3/2/0	5/3/1/0	0.83
HFrEF/HFpEF/HFmEF	3/5/0	2/4/3	0.35
Type 2 diabetis mellitus	3	2	0.62
CAD	4	8	0.13
Pacemakers/CID	3	1	0.29
Vasodilatator treatment	2	1	0.58
Anticoagulantia	3	4	1
B-blockers	7	9	0.47
Diuretics	6	4	0.33
Statins	4	8	0.13
ACE inhibitors	4	8	0.13
Etiology (Ischemic/hypertension/valvula/ problem unknown)	5/1/2/0	8/0/0/1	0.19

Data is presented as mean ± standard deviation. N= number of participants who are included in the data.
LVEF%= left ventricular ejection fraction. BMI= body mass index.
VO2peak = peak oxygen uptake. NYHA= New York Heart association classification.
HFrEF= heart failure with reduced ejection fraction. HFpEF= heart failure with preserved ejection fraction.
HFmEF= heart failure with “mid-range” ejection fraction CAD= coronary artery disease.
ICD= implantable cardioverter-defibrillator. ACE= Angiotensin-converting enzyme
P values represented are the result of a student t-test for age, LVEF%, BMI and VO2peak.
All other P-values were calculated using fisher’s exact test

Table 2

FMD measurement

	HIIT (N=5)				CT N=4				P-values			
	Before		After		Before		After		Within group		Between group	
	Mean		Mean		Mean		Mean		HIIT	CT	Before	After
Diameter rest (mm)	4.54	± 1.09	4.54	± 0.93	4.36	± 1.18	4.35	± 0.51	1.00	0.99	0.82	0.74
Peak diameter (mm)	4.77	± 1.10	4.75	± 0.88	4.54	± 1.11	4.58	± 0.39	0.94	0.92	0.77	0.74
FMD (%)	5.37	± 2.59	5.01	± 3.94	4.62	± 2.60	5.51	± 3.61	0.87	0.37	0.68	0.85
Velocity rest (cm/s)	16.78	± 10.88	20.74	± 4.65	19.83	± 8.87	23.54	± 11.75	1	0.99	0.67	0.72
Hyperemic velocity	58.82	± 33.69	37.39	± 29.04	59.95	± 15.70	78.18	± 15.14	0.20	0.27	0.95	0.15

Note: Data for eight participants was lost and is not included this table. Data was available for five HIIT participants and four CT group participants.
Data is presented as mean ± standard deviation. N= number of participants who are included in the data. FMD%= flow mediated dilation expressed in percentage.
Within group P-values refer to the paired student T-test or Wilcoxon signed rank test when appropriate.
Between group P-values refer to independent student T-test or Wilcoxon's rank sum test.
* significantly different at $P < 0.05$

Table 3

Across group effects

	Group	Time	Group*time
FMD	0.95	0.83	0.62
SDNN	**0.004***	0.16	0.39
Rrtri	**0.0003***	0.32	0.74

Data represented are p-values of repeated measurements analysis of variance

* significantly different at $p<0.05$

Table 4

Correlations between main outcomes at baseline

	VO2peak TBW	VO2peak	VE/VCO2 Slope	RMSSD	SDNN	Rrtri	FMD%
VO2peak TBW	--						
VO2peak	**0.74***	--					
VE/VCO2 Slope	0.08	0.10	--				
RMSSD	-0.25	-0.26	0.20	--			
SDNN	-0.11	-0.10	0.51	**0.90***	--		
Rrtri	-0.11	-0.14	0.40	**0.83***	**0.82***	--	
FMD%	0.14	-0.37	0.05	0.59	0.59	0.59	--
LVEF%	0.31	0.31	-0.18	**-0.54***	-0.33	-0.25	-0.10

Numbers represented are Pearson's correlation coefficient

*significant at $p<0.05$

Table 5

CPET

	HIIT (N=8)		CT (N=9)		P-values			
	Before	After	Before	After	Within group		Between group	
	Mean	Mean	Mean	Mean	HIIT	CT	Before	After
Pmax (W)	97 ± 26	115 ± 35	126 ± 34	130 ± 40	**0.02***	0.48	0.07	0.41
RERpeak	1.24 ± 0.12	1.18 ± 0.07	1.23 ± 0.12	1.20 ± 0.02	0.22	0.44	0.94	0.46
VO2peak TBW (ml/kg/min)	17.47 ± 4.22	19.64 ± 4.89	21.07 ± 4.13	21.43 ± 5.62	**0.03***	0.67	0.10	0.74
VO2peak (ml/min)	1437 ± 411	1563 ± 446	1659 ± 459	1675 ± 517	0.09	0.79	0.31	0.64
VE/VCO2 slope	28.97 ± 6.37	31.9 ± 5.75	28.46 ± 6.64	32.27 ± 2.17	0.22	**<0.01***	1	0.66

Data is presented as mean ± standard deviation. N= number of participants who are included in the data. Pmax= peak power in Watt. RERpeak= Respiratory exchange ratio. VO2peak TBW= peak oxygen uptake compared to total body weight. VO2peak= peak oxygen uptake. VE/VCO2= minute ventilation/carbon dioxide production.
Within group P-values refer to the paired student T-test or Wilcoxon signed rank test when appropriate.
Between group P-values refer to independent student T-test or Wilcoxon's rank sum test.
* significantly different at $P < 0.05$

Table 6

Adjustment for baseline

	Intervention	Baseline effect
VO2peak TBW	**0.048***	**<0.01**
VO2peak	0.21	**<0.01**
VE/VCO2 slope	0.50	**<0.01**
RMSSD	0.23	0.10

Data represented are p-values of analysis of covariance (ANCOVA)

* significantly different at p<0.05

Table 7

HRV measurements

	HIIT				CT				P-values			
	Before		After		Before		After		Within group		Between group	
	Mean		Mean		Mean		Mean		HIIT	CT	Before	After
Mean RR (ms)	909	± 39	926	± 67	873	± 123	907	± 169	0.56	0.73	0.16	0.44
SDNN	36.6	± 12.74	29.38	± 7.36	22.32	± 7.44	20.5	± 6.64	0.22	0.62	0.02*	**0.03***
RMSSD	37.7	± 19.04	32.85	± 15.12	19.72	± 9.09	17.51	± 8.36	0.46	0.61	**0.03***	**0.02***
Rrtri	9.62	± 2.42	8.89	± 2.44	6.04	± 1.99	5.47	± 1.39	0.50	0.52	**<0.01***	**<0.01***

Data is presented as mean ± standard deviation. N= number of participants who are included in the data. Mean RR= the mean interval between R-waves. SDNN= standard deviation of intervals between normal R-waves. RMSSD= root mean square of successive RR interval difference. Rrtri= triangular index.
Within group P-values refer to the paired student T-test or Wilcoxon signed rank test when appropriate.
Between group P-values refer to independent student T-test or Wilcoxon's rank sum test.
* significantly different at $p<0.05$

www.uhasselt.be
Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
11/10/2020	Overleg onderwerp MP2	Promotor: Kenneth Verboven Copromotor/Begeleider: Student(e): Student(e):
11/12/2020	Mail dataset	Promotor: Kenneth Verboven Copromotor/Begeleider: Student(e): Student(e):
17/12/2020	Mail met uitleg over dataset	Promotor: Kenneth Verboven Copromotor/Begeleider: Student(e): Student(e):
30/12/2020	Verbetering 1e versie	Promotor: Kenneth Verboven Copromotor/Begeleider: Student(e): Student(e):
02/01/2020	Verbetering 2e versie	Promotor: Kenneth Verboven Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): …… Datum:……..

Titel Masterproef: ……

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	**NVT**	**1**	**2**	**3**	**4**	**5**
Opstelling onderzoeksvraag	O	O	O	O	Ø	O
Methodologische uitwerking	O	O	O	O	Ø	O
Data acquisitie	Ø	O	O	O	O	O
Data management	O	O	O	O	Ø	O
Dataverwerking/Statistiek	O	O	O	O	Ø	O
Rapportage	O	O	O	O	Ø	O

2) Niet-bindend advies: Student(e) krijgt toelating/~~geen toelating~~ (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) openbaar verdedigd worden.

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/~~niet~~ (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

Datum en handtekening Student(e)	Datum en handtekening promotor(en)	Datum en handtekening Co-promotor(en)
02/01/2021	03/01/2021	