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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Master Thesis Part 2: What is the influence of resistance training on endothelial function in heart failure patients?

Ruben Kerkhofs

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

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Acknowledgement:

First of all, special thanks go to my promotor, dr. Verboven Kenneth, for the fruitful cooperation during the course of this thesis. I would also like to thank all the involved researchers from the *Universidade de Brasília (Brazil)*, for collecting and providing the data that were used and processed within this explorative study.

Wolfsstraat 50, Oudsbergen, 07/06/2021 R.K.

Context:

Cardiovascular disease is, globally speaking, the leading cause of death (World Health Organization, (2017)). This collective term also encapsules heart failure: a condition that is caused by structural and/ or functional anomalies of the heart, significantly impairing the cardiac output and/ or intracardiac pressure during ortho- and/ or parasympathetic activity.

Current guidelines by the *Heart Failure Association* and the *European Association for Cardiovascular Prevention and Rehabilitation* recommend the implementation of continuous endurance training at a moderate intensity, performed on a regular basis (Rees et al., (2001): Ashor et al., (2015): Ramos et al., (2015): Piepoli et al., (2011): Corra et al., (2010): Ponikowski et al., (2016)). However, limited research has provided empirical evidence that other exercise modalities yield superior results within this population, compared to continuous endurance training (Wisloff et al., (2007): Ramos et al., (2015)).

The effects of continuous endurance training on a spectrum of outcome measures have been researched extensively within the heart failure population. However, a lack of empirical evidence was discovered when it comes to evaluating the effects of resistance training on the functionality of the endothelium within this population. The importance of the endothelial function lies in its influence on the severity of heart failure and rate of cardiovascular-related mortality (Alem et al., (2019): Ponikowski et al., (2016): Bauersachs et al., (2008): Giannitsi et al., (2019)). More research concerning the effectiveness of this exercise modality may contribute to a more optimized treatment protocol within the heart failure population.

This thesis, which is considered to be a part of the rehabilitation of internal disorders, is supervised by promotor dr. Verboven Kenneth, and by co-promotor Prof. dr. Hansen Dominique, and is considered a small part within a larger project that is aiming to research the influence of high intensity interval training, and resistance training on endothelial function, and physical fitness in heart failure patients.

The *Universiteit Hasselt* has provided a central format, which served as a guideline to write this thesis. The study protocol has been co-created by researchers from the *Universiteit Hasselt (Belgium)*, and researchers from the *Universidade de Brasília (Brazil)*. Recruitment of participants, exercise interventions, and data collection occurred during the academic year 2019 – 2020, at the *Universidade de Brasília*. Statistical analysis and the writing of this thesis was performed by Ruben Kerkhofs, during the academic year 2020 – 2021, under supervision of dr. Verboven Kenneth.

1. Abstract:

Background

Blood vessels consist of different layers, the innermost layer being the endothelium. EC are important in blood flow regulation. This is effectuated through the release of NO, resulting in vasodilation. This process is important in supplying oxygen to peripheral tissues during physical activity. In HF patients, a decreased LVEjF causes a diminution of arterial blood flow, resulting in an impaired exercise tolerance. This explorative study came to be because research concerning the effects or RT on EF in stable HF patients is limited.

Objective

To investigate the influence of resistance training on endothelial function, quantified through brachial artery flow-mediated dilation, in stable heart failure patients.

Methods

53 Patients with stable heart failure were recruited through local hospitals and heart failure clinics at the *Universidade de Brasília*. In total, 18 subjects met eligibility criteria and were randomly allocated to one of the following groups: the resistance training group or the control group. The intervention group performed three supervised exercise sessions per week, for 12 weeks. For every group, the following primary outcomes were assessed at baseline, and after three months of training: endothelial function, muscle mass, and muscle force.

Results

At baseline, both groups were comparable with regard to their descriptive characteristics. The intervention did not elicit significant changes in EF. Among these outcome measures are: brachial artery FMD, peak and resting diameter of the brachial artery, and the conductance velocities of the blood vessels at rest and during the hyperaemic response to the release of the sphygmomanometric cuff.

Conclusion

The exercise intervention induced a significant increase in muscle force. However, endothelial function was not affected. Considering several limitations, it is unlikely that these findings are representative for determining the effect(s) of circuit-based resistance training interventions in the heart failure population.

Keywords

Heart failure, endothelial function, resistance training.

2. Introduction:

Heart failure (HF), a condition that is caused by structural and/ or functional anomalies of the heart, significantly impairing the cardiac output and/ or intracardiac pressure during ortho- and/ or parasympathetic activity. This cardiovascular disease is characterized by breathlessness at rest and/ or during physical activity, ascites, fatigue, and a diminished left ventricular ejection fraction (LVEjF) among others (Ponikowski et al., (2016)).

Recent evidence has provided information that estimates the current global prevalence of HF is ranging between 1% and 14%. Regardless of an augmented awareness about this leading cause of death, globally speaking, multiple studies have reported that the prevalence of cardiovascular disease will increase to 30% by the year 2030 in the United States of America (Heidenreich et al., (2013): Dunlay et al., (2014): World Health Organization, (2017)). This continuous, problematic increase in prevalence is accompanied by staggeringly poor long- and short-term mortality rates in the HF population. In acutely hospitalized patients, the mortality rate lies between 5.8% and 8.1%. Furthermore, the survival rate, five years after diagnosis is only 57% within this population (Guha et al., (2013): Hobbs et al., (2007): Nieminen et al., (2006): Nicol et al., (2008)).

Extensive research has repeatedly shown that exercise therapy (ET) significantly influences a variety of other important factors that are associated with HF: improving exercise capacity, endothelial function (EF), maximal oxygen consumption, health-related quality of life, lowering the number of hospital admissions… (Rees et al., (2001): Ashor et al., (2015): Ramos et al., (2015): Piepoli et al., (2011)). The most recent guidelines, written by the *Heart Failure Association* and the *European Society of Cardiology*, provide the common exercise modalities, used to achieve the aforementioned improvements. Four different categories can be distinguished: continuous endurance training (CET), interval training (IT), resistance training (RT), and respiratory training (ReT) (Ponikowski et al., (2016)). It is recommended that rehabilitation in all HF patients should involve regular CET in order to improve functional capacity and symptoms among others (Ponikowski et al., (2016)). However, multiple studies have provided empirical evidence that IT yielded significantly greater improvements in cardiorespiratory fitness and EF within the HF population, compared to CET (Wisloff et al., (2007): Ramos et al., (2015)). Furthermore, limited evidence in a meta-analysis by Ashor et al.

suggests that RT also significantly increases EF in different populations, including coronary artery disease and HF populations (Ashor et al., (2015)).

The previously mentioned EF is highly dependent on endothelial cells (EC): the innermost layer of blood vessels. These cells are particularly important when it comes to blood flow regulation: this occurs through the release of nitric oxide (NO), resulting in the vasodilation of the affected vessel. In HF, the blood flow in peripheral and conductance arteries is reduced, and the ventricular function is inherently impaired: these systemic changes result in a diminished exertion of shear stress on the luminal wall, which effectively means less endothelial NO is synthesized. This cascade results in a decreased endothelium-dependent vasodilation, partially responsible for a diminished peripheral oxygen supply, inciting an impaired exercise tolerance within this population (Bauersachs et al., (2008): Giannitsi et al., (2019): Ramanlal et al. (2021)). Performing physical exercise on a regular basis causes physiological changes to occur in the EC: an increase in flow-mediated shear stress will activate a complex signalling cascade, resulting in an augmented synthesis of endothelial NO, thus increasing its availability during physical activity (Kojda et al., (2005)). This increase in flow-mediated shear stress is a direct result of different exercise therapy modalities, performed at a sufficiently high exercise intensity (Ramos et al., (2015): (Ashor et al., (2015): (Hallmark et al., (2014): McClean et al., (2015)).

In maltreated patients, the severity of HF can increase over time. One of the key components in this process of deterioration is a diminished EF. In theory, endothelium-dependent vasodilation can be assessed through both invasive and non-invasive methods. The former methods aim to infuse vasoactive compounds that mimic the aforementioned endothelium-dependent vasodilation. Next, the response is observed. Non-invasive alternatives, used to quantify EF, consist of: brachial artery flow-mediated dilation (FMD), and venous occlusion digital plethysmography among others (Giannitsi et al., (2019)).

While a vast number of studies have extensively researched the various effects of ET on a spectrum of outcome measures within the HF population, the previously performed literature study, linked to this RCT, concluded a lack of research in the following domain is present: *“What is the influence of resistance training on endothelial function in heart failure patients?”*. Therefore, this is the research question that should be posed.

3. Methods:

- Participants

This explorative randomized controlled trial originally consists of three groups, monitored over a 12-week period: a resistance training group (RTG), a high intensity interval training group (HIITG), and the control group (CG). Each of the groups was assessed at baseline, and three months after baseline in an attempt to detect changes over time. A total of 53 subjects were recruited through local hospital databases and HF clinics at the *Universidade de Brasília*. After the screening of all potential participants took place, 21 patients were considered ineligible in regard to the exclusion criteria and five potential subjects were unwilling to take part in this study. Inclusion criteria for this RCT included 1) men and women of 35 years or older, 2) diagnosis of heart failure reduced ejection fraction (HFrEjF) for at least six months, or heart failure preserved ejection fraction (HFpEjF) for at least six months, 3) being medically stable for at least the past three months, and 4) an ischaemic, hypertensive, or idiopathic onset of HF. Exclusion criteria for this RCT: 1) FEV_1< 50%, 2) inflammatory disease, 3) Chagas disease, 4) lesions of muscular, orthopaedic or joint-related nature that prohibit participation in an exercise intervention, 5) patients with a pacemaker, or an implantable cardioverter defibrillator, 6) smokers, 7) participation in structured physical activity in the past six months, and 8) pregnancy. The 27 remaining participants were randomly allocated to one of three groups, using closed envelopes. Due to the nature of the intervention, participants could not be blinded. However, the assessors for all outcome measures were blinded. Eventually, 15 out of 18 subjects managed to complete the study. Three participants, all of which were allocated to the RTG, dropped out during the randomized controlled trial because of issues related to commuting (n=3). Information with regard to subject characteristics can be found in Table 1. This study report only contains data from the CG and the RTG: the HIITG will not be analysed in this randomized controlled trial.

The study protocol for this RCT was approved by the Ethics Committee of the *Universidade de Brasília*, and was executed according to the Declaration of Helsinki, 2013. A written informed consent was provided to each of the participants, prior to the start of the experimental procedures. Trial registration number: RBR-668c8v.

- Intervention

The intervention for the RTG consisted of a 12-week exercise program, at a training frequency of three sessions per week. The exercises that were performed during every session were: 1) pull down, 2) leg press, 3) arm press, 4) shoulder press, 5) leg extension and 6) leg flexion. Every training session was initiated by doing a ten minute warming-up: five minutes of stretching, followed by five minutes of dynamic exercises. During the first six sessions, participants performed three sets of each exercise for 12 repetitions, at an intensity of 50% of the one repetition maximum (1-RM). In weeks 3 and 4, exercise intensity was increased to 60% 1-RM, and the aim was to achieve 15 – 20 repetitions during each set. In weeks 5 and 6, exercise intensity was increased to 70% 1-RM, and the aim was to achieve 6 – 12 repetitions during each set. In weeks 7 and 8, exercise intensity remained at 70% 1-RM, and the aim was to achieve 15 – 20 repetitions during each set. In weeks 9 and 10, exercise intensity was increased to 80% 1-RM, and the aim was to achieve 6 – 12 repetitions during each set. In weeks 11 and 12, exercise intensity remained at 80% 1-RM, and the aim was to achieve 15 – 20 repetitions during each set. All of the exercises were performed in resistive stations (EN-Dynamic, Enraf-Nonius, Rotterdam, Netherlands). A resting interval of 60 seconds was used for consecutive exercises, until one set of every exercise was completed. This cycle was repeated until the participant performed three sets for each exercise. Every exercise session was supervised by a group of physiotherapists. Multiple physiological factors, such as heart rate and blood pressure, were checked prior to, and after every training session, to further guarantee patient safety. This data is not reported in this study.

The CG did not receive an intervention. The participants in this group were advised to maintain their usual level of activity, and lifestyle.

- Procedure
    - Primary Outcome Measure
        - Endothelial Function

The primary outcome measure that was assessed in this randomized controlled trial is EF, measured through brachial artery FMD. This non-invasive technique quantifies the endothelial function through measuring the change in arterial diameter of the brachial artery, provoked by the release of NO. This change is assessed through the use of B-mode ultrasound imaging (Philips, Amsterdam, Netherlands, HD11XE, 7.5 MHz Linear Matrix Transducers) and is expressed as a percentage increase. As a part of the preparations for this assessment, participants were informed to consume a small meal at least two hours before testing. Furthermore, subjects were asked to abstain from: 1) caffein intake, 2) alcohol use, and 3) physical activity in the 48 hours that preceded the examination. Every assessment was conducted on the right arm, in a room with a temperature of 24 degrees Celsius, at the same time of day to minimize the involvement of the circadian rhythm.

First, a baseline measurement of the brachial artery diameter (BAD) was acquired through B-mode Ultrasound Imaging. To achieve this, the patient is positioned supine. A sphygmomanometric cuff is placed slightly distally to the proximal radio-ulnar joint. Next, the participant is given a 10-minute resting period. Five minutes into the rest period, the subject's blood pressure is assessed by using a non-invasive oscillometric blood pressure monitor. Next, a cross-sectional scan of the brachial artery is performed in the antecubital fossa, so that the artery is aligned with the longitudinal axis.

After the baseline measurement, the aforementioned cuff will be inflated to 220 mmHg for five minutes. After four minutes 30 seconds have expired, attempt to bring the probe into the correct position again to perform another cross-sectional scan of the brachial artery in the antecubital fossa, so that the artery is aligned with the longitudinal axis. Start the recording after four minutes 50 seconds have expired. Next, release all the pressure from the sphygmomanometric cuff, and record until three minutes after rapid cuff deflation (Alley et al., (2014)). Afterwards, analysis of the images were performed by using specialized edge-detection software (Cardiovascular Suite). All assessments regarding EF were performed and analysed by a single researcher. The brachial artery FMD is expressed as a percentage increase of the peak diameter compared to the resting diameter, both measured using the metric system. Conductance velocities within the blood vessels are measured in cm/s.

- Secondary Outcome Measures:
  - Muscle Force:

Muscle force (MF) consisted of two separate measurements, the first of which is an isometric and isokinetic strength assessment of m. quadriceps femoris, using the BioDex System 3 PRO (Medical Inc., New York, US). First, the subject was placed in a seated position, with 90° hip flexion and belt fixations of the trunk, thighs, and pelvis. Next, to get the participant acquainted with the test, three voluntary, isometric, submaximal contractions were performed for five seconds, with 30 seconds between each repetition. Afterwards, five voluntary, isometric, maximal contractions were performed for five seconds, with 30 seconds between each repetition. The value of the highest maximal voluntary, isometric contraction was used for data analysis. After the five voluntary, isometric, maximal contractions, the participant rested for three minutes. Next, participants were introduced to the isokinetic test by performing six repetitions at a velocity of 180°/s. Afterwards, each subject had one attempt to complete the isokinetic assessment: 20 repetitions at a velocity of 180°/s. In both tests, peak torque was measured in Nm/kg. The average power during the isokinetic test was measured in W. The second measurement consisted of a 1-RM test for the: 1) pull down, 2) leg press, 3) arm press, 4) shoulder press, 5) leg extension and 6) leg flexion, performed according to the testing protocol, described by the American College of Sports Medicine (ACSM). Throughout the complete duration of this RCT, no retesting of the 1-RM occurred.

- Muscle Mass:

Muscle mass (MM) was quantified by performing B-mode Ultrasound Imaging (Philips, Amsterdam, Netherlands, HD11XE, 7.5 MHz Linear Matrix Transducers) on the m. quadriceps femoris, in order to assess the thickness of the m. rectus femoris, and m. vastus intermedius. First, the subject was placed in a supine position, with a passive flexion of the right knee. Next, an echographic lubricant was applied to the probe to avoid any direct contact with the skin. The probe was positioned perpendicular to the orientation of the m. quadriceps femoris of the right leg at all times, while moving between the anterior superior iliac spine and the patella base. Afterwards, analysis of the imaging occurred though ImageJ processing software. The muscle thicknesses of m. rectus femoris and m. quadriceps femoris were measured using the metric system.

- Data Analysis:

Statistical analyses were performed using JMP Pro 15, by the SAS Institute. All of the provided data are reported as mean $\pm$ standard error of the mean (SEM), unless otherwise specified. In this randomized controlled statistical significance is assumed at $P< 0.05$. All base assumptions were evaluated and satisfied, among which are homoscedasticity (Brown – Forsythe Test), normality of the residuals (Goodness of Fit Test), and independency of measurements. For within-group differences, analyses were performed using mixed models with repeated measures (Student's t All Pairwise Comparisons). For between-group differences, analyses were performed using ANOVA (Wilcoxon Rank Sum Exact Test) and contingency tables (Fisher Exact Test).

4. Results:

- Baseline Characteristics:

At baseline, VO_2-Peak (ml/$kg_{Bodyweight}$/min) was significantly higher in the CG. This can possibly be attributed to the higher average body mass index (BMI) in the RTG, although the difference is not significant (**RTG**: 32.93 ± 2.1598 kg/m², **CG**: 28.30 ± 1.7635 kg/m²; P= 0.2159). No other significant differences were detected between the RTG and the CG at this point in time. Table 1 contains a complete display of factors, assessed at baseline.

- Endothelial Function:
    - Brachial Artery Flow-mediated Dilation:

The exercise program was not able to elicit a significant improvement in any outcome measure related to EF in the RTG. Most importantly, brachial artery FMD was not significantly affected by the intervention within the 12 week period (4.54 ± 1.07 % versus 4.96 ± 1.72 %; P= 0.8087). The increase in brachial artery FMD was greater in the CG when compared to the RTG, but insignificant nonetheless (4.62 ± 1.32 % versus 5.51 ± 2.10 %; P= 0.8321). The other outcome measures that were related to EF were not significantly influenced in either group over the 12 week period of this randomized controlled trial. Among these are: the resting diameter of the brachial artery, the peak diameter of the brachial artery and the conductance velocities of the blood vessels at rest and during the hyperaemic response to the release of the sphygmomanometric cuff. Table 2 contains a complete display of data regarding EF assessments.

- Muscle Force:
    - BioDex:

In the RTG, statistical analysis revealed that the prescribed exercise intervention significantly increased the average power during the isokinetic test (177.13 ± 26.41 W versus 191.12 ± 26.22 W; P= 0.0391). Despite the absence of a within-group difference in the CG (167.63 ± 26.42 W versus 169.03 ± 26.22 W; P= 0.87), average power during the isokinetic was not significantly higher in the RTG (P= 0.2176). Data concerning the peak torque during the isokinetic and isometric tests, relative to the lean muscle mass of the right leg, was not significantly affected in either group. Table 2 contains a complete display of data regarding BioDex assessments.

- One Repetition Maximum:

Mixed model ANOVA revealed that the 1-RM for the leg press exercise significantly improved in both groups (**RTG**: 97.50 ± 11.03 kg versus 113.00 ± 13.87 kg; P= 0.0298, **CG**: 75.60 ± 12.0870 kg versus 95.00 ± 15.19 kg; P= 0.0393). The increase, elicited in the RTG, was not significantly different compared to the CG (P= 0.6429). The 1-RM for the arm press exercise also significantly improved exclusively in the RTG (61.50 ± 7.01 kg versus 74.25 ± 8.88 kg; P= 0.0190). None of the 1-RM's for the other exercises significantly increased or differed within and between both groups respectively. Among these exercises are: the shoulder press, the pull down, the leg extension, and the leg flexion. Table 2 contains a complete display of data regarding 1-RM assessments.

- Muscle Mass:
    - Ultrasound:

After 12 weeks, no significant echographic changes of both the m. quadriceps and the m. rectus femoris were detected in either group, indicating the absence of a substantial increase in MM (**RTG**: 3.40 ± 0.40 cm versus 3.79 ± 0.47 cm; P= 0.261, and 1.91 ± 0.16 cm versus 2.09 ± 0.20 cm; P= 0.1173, **CG**: 3.69 ± 0.28 cm versus 3.69 ± 0.39 cm; P= 0.6926, and 2.00 ± 0.13 cm versus 2.06 ± 0.18 cm; P= 0.253). No other significant changes were detected concerning the MM assessments. Table 2 contains a complete display of data regarding ultrasound assessments.

5. Discussion:

- Reflections:

The main goal of this randomized controlled trial was to evaluate the isolated effect of a progressive, circuit-based resistance training intervention on EF in a sample that is representative of the HF population. The findings showed that, generally, strength increased in the RTG. However, this intervention was not able to elicit a significant increase in EF within the aforementioned sample. This suggests that progressive, circuit-based resistance training is not effective in improving EF in the HF population. It is a fact that, at this point in time, research concerning the possible effect(s) of RT on EF is very limited in the aforementioned population. Thus, this explorative study does not serve as conclusive evidence for this statement to be substantiated or rejected.

Previously, research even claimed that isolated RT results in unfavourable outcomes concerning EF. Multiple large, long-term interventional studies detected that RT, regardless of the exercise intensity, resulted in a reduction of arterial compliance, while simultaneously increasing the arterial stiffness in a young, and healthy population (Cortez-Cooper et al., (2005): Miyachi et al., (2004)). Arterial compliance, the extent to which arteries can adapt to different intravascular pressures, is altered in a multitude of pathological circumstances, among which are hypertension, atherosclerosis, and HF (Glasser et al., (1997): Frostegård et al., (2013)). The diminution in arterial compliance has been attributed to changes in the elastin and collagen composition of the arteries, an adaptation that also possibly occurs as a result of RT. Even so, the changes that RT elicited in this population normalized after a period of detraining. Although the aforementioned statements have never been refuted by empirical evidence, additional research has suggested that the combination of aerobic exercise and RT prevents this regression in arterial compliance from occurring. Furthermore, a trend towards an increase in arterial compliance was detected upon the inclusion of aerobic training during the exercise intervention (Kawano et al., (2006)).

In 2011, Maiorana et al. claimed that a progressive resistance training intervention induced systemic vascular remodelling in the HF population: a significant decrease in brachial artery wall thickness (BAWT) was detected, along with a significant increase in BAD (Maiorana et al., (2011)). The randomized controlled trial by Anagnostakou et al. substantiates these findings: the combination of resistance training and interval training was found to be significantly better

concerning the improvement of brachial artery FMD over the course of three months, compared to isolated interval training in the HF population (Anagnostakou et al., (2011)). Furthermore, the latter exercise modality did not elicit a significant improvement in brachial artery FMD (Anagnostakou et al., (2011)). However, research by Zoeller et al. refutes the claim that resistance training has the potency to induce systemic vascular changes. In the aforementioned trial, healthy untrained individuals performed unilateral resistance training over a period of three months. While the BAD in the trained arm significantly increased over the course of the intervention, the BAD in the untrained arm was not significantly influenced. Thus, it is likely that resistance training only induces regional vascular remodelling (Zoeller et al., (2009)).

Several lines of thought are present when attempting to pinpoint the potential pathway, responsible for the angiogenic changes, elicited by ET. It is known that regional vascular changes are elicited through the upregulation of the VEGF protein, responsible for the growth of capillaries. Increased VEGF mRNA transcription can be accomplished through attaining a low partial oxygen pressure in the activated muscle(s). The magnitude of this upregulation depends on two factors: the time after the exercise bout and the intensity of the exercise bout. As for the time-related factor, there is a negative correlation with the upregulation of VEGF mRNA transcription. As for the intensity-related factor, there is a positive correlation with the upregulation of VEGF mRNA transcription (Prior et al., (2003)). During resistance training, fast glycolytic fibers are responsible for the short, forceful contractions. These anaerobic processes could be responsible for the lack of significant change in EF within this randomized controlled trial. On the other hand, vascular changes can occur through the endothelial mechanotransduction mechanism: a vascular, homeostatic system that detects changes in shear stress, activated by physical activity among others (Kojda et al., (2005)). This change in shear stress between the blood and the EC activates endothelial mechanosomes: mechanoreceptors, built into the membrane of the EC. In turn, a complex signaling cascade is triggered, responsible for: vascular remodelling, regulating angiogenesis, and increasing NO production among other antiatherogenic effects (Kojda et al., (2005): Chatterjee et al., (2018): Garoffolo et al., (2019)). In-depth research concerning the physiology of these various pathways could possibly reveal the actual, underlying processes that are activated in response to the different modalities of exercise. This knowledge could further facilitate research regarding the effectiveness of different exercise modalities within the HF population.

- Limitations:

This randomized controlled trial was subject to several issues. First, the number of recruited participants for each of the samples was relatively small. This meant two things: drop outs would continue to distort possible effects, and non-parametric statistical analysis had to be applied, which rejects the normal distribution of each sample.

In total 33% of the participants, originally allocated to the RTG, dropped out: this indicates the presence of a significant attrition bias. Furthermore, significant data loss occurred: the data pool from an already limited sample became even more limited. This was attributed to the complexity of the assessments. Table 3 contains a complete display of the occurrence of data loss.

Lastly, the participants' adherence to the intervention was not monitored. A lack of adherence to the progressive, circuit-based resistance training intervention could have negatively influenced the amount of progression, made by the RTG, concerning the strength-related outcome measures among others.

- Conclusion:

This randomized controlled trial was not successful in eliciting a significant increase in EF in HF patients through and isolated, progressive, circuit-based resistance training intervention. More high quality research is needed to definitively determine the effects of this exercise modality on EF, within the aforementioned population.

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8. Appendices:

Table 1: Overview of the baseline characteristics for both samples.

	RTG (n=6):	**CG (n=9):**	**P-value:**
Sex (m):	4	8	0.5253
Etiology (IC: HP: RA: ID: HV):	4:1:0:1:0	8:0:0:0:1	0.3407
HF (HFrEjF: HFmEjF: HFpEjF):	3:2:1	2:3:4	0.8002
NYHA (I: II: III: IV):	2:3:1:0	5:3:1:0	0.7902
Hypertension (Y):	4	4	0.6084
Diabetes Mellitus (Y):	3	2	0.3287
Dyslipidemia (Y):	5	7	1.0000
CAD (Y):	4	8	0.5253
BMI (N: Ov: Ob):	0:2:4	2:3:4	0.4825
CABG (Y):	1	3	0.2867
Coronary Angioplasty (Y):	0	0	1.0000
Heart Valve Surgery (Y):	1	3	0.6044
Pacemaker/ ICD (Y):	1	1	1.0000
Anti-acid Treatment, Stomach (Y):	1	2	1.0000
Vasodilator Treatment (Y):	0	1	1.0000
Anti-coagulating Agents, Platelets (Y):	5	4	0.2867
Anti-arhythmia Treatment (Y):	0	2	0.4857
Anti-coagulating Agents (Y):	0	2	0.4857
Medication, Diabetes Mellitus (Y):	2	2	1.0000
Beta-blockers (Y):	5	9	0.4000
Calcium Channel Antagonists (Y):	0	0	1.0000
Diuretics (Y):	1	4	0.2867
Statine Treatment (Y):	5	8	1.0000
Bradycardia (Y):	1	2	1.0000
ACE-inhibitors (Y):	4	8	0.5253
Age (years):	55 $\pm$ 4.3612	54 $\pm$ 3.5609	0.8597
Septal Wall e' (cm/s):	5.0 $\pm$ 0.5573	5.4 $\pm$ 0.4550	0.5008
Lateral Wall e' (cm/s):	8.2 $\pm$ 1.2852	9.3 $\pm$ 1.0494	0.6756
Ejection Fraction (%):	42.2 $\pm$ 5.5220	47.2 $\pm$ 4.5087	0.3449
BMI (kg/m^2):	32.9 $\pm$ 2.1598	28.3 $\pm$ 1.7635	0.2159
VO_2-peak ($ml/kg_{Bodyweight}/min$):	16.9 $\pm$ 1.4671	21.1 $\pm$ 1.1979	0.0449
NT-ProBNP (pg/ml):	380.7 $\pm$ 245.26	801.5 $\pm$ 245.26	0.2290
LAVI (ml/m^2):	31.7 $\pm$ 3.6089	33.0 $\pm$ 2.9467	0.9530
LVMI (g/m^2):	107.6 $\pm$ 8.6936	99.1 $\pm$ 7.0983	0.3165

RTG= Resistance Training Group, CG= Control Group, m= Male, IC= Ischemic, HP= Hypertension, RA= Rheumatoid Arthritis, ID= Idiopathic, HV= Heart Valves, Y= Yes, HF= Heart Failure, HFrEjF= Heart Failure Reduced Ejection Fraction, HFmEjF= Heart Failure Mid-range Ejection Fraction, HFpEjF= Heart Failure Preserved Ejection Fraction, I= NYHA I, II= NYHA II, III= NYHA III, IV= NYHA IV, NYHA= New York Heart Association Classification, CAD= Coronary Artery Disease, BMI= Body Mass Index Classification, N= Normal BMI, Ov= Overweight BMI, Ob= Obese BMI, CABG= Coronary Artery Bypass Graft, ICD= Implantable Cardioverter Defibrillator, BMI= Body Mass Index, NT-ProBNP= N-terminal Prohormone of Brain Natriuretic Peptide, LAVI= Left Atrial Volume Index, LVMI= Left Ventricular Mass Index.

Table 2: Overview of the data for EF, MF, and MM respectively.

	RTG, T_0 (n=6):	**RTG, T_1 (n=6):**	**P-value (W):**	**CG, T_0 (n=9):**	**CG, T_1 (n=9):**	**P-value (W):**	**P-value (B):**
Diameter Rest (mm):	4.38 ± 0.3475	4.52 ± 0.2348	0.4337	4.36 ± 0.4256	4.35 ± 0.2875	0.9848	0.6775
Velocity Rest (cm/s):	22.14 ± 3.1576	14.80 ± 3.8126	0.1057	19.83 ± 3.8673	23.55 ± 4.4025	0.0649	0.0510
Velocity Hyperaemic (cm/s):	81.96 ± 9.3380	72.78 ± 14.7030	0.4993	59.95 ± 11.437	78.18 ± 16.9770	0.2188	0.2238
Peak Diameter (mm):	4.57 ± 0.3373	4.74 ± 0.2081	0.2360	4.54 ± 0.4131	4.58 ± 0.2549	0.9199	0.7294
FMD (%):	4.54 ± 1.0743	4.96 ± 1.7204	0.8087	4.62 ± 1.3158	5.51 ± 2.1071	0.3667	0.8321
PT Isom/Lean Mass Right Leg (Nm/kg):	22.26 ± 2.1691	24.39 ± 2.5359	0.5178	22.62 ± 2.1691	23.92 ± 2.5359	0.3088	0.7985
PT Isok/Lean Mass Right Leg (Nm/kg):	13.55 ± 1.3467	14.79 ± 1.6330	0.5703	14.02 ± 1.3467	13.74 ± 1.6330	0.6730	0.4819
AVG Power, Isok (W):	177.13 ± 26.4190	191.12 ± 26.2190	0.0391	167.63 ± 26.4190	169.03 ± 26.2190	0.8700	0.2176
Pull Down (kg):	38.8 ± 2.2680	48.4 ± 4.9145	0.0662	41.2 ± 4.6753	43.5 ± 5.3835	0.5826	0.2337
Arm Press (kg):	61.5 ± 7.0688	74.3 ± 8.8785	0.0190	63.8 ± 7.7435	67.3 ± 9.7259	0.6075	0.2202
Shoulder Press (kg):	43.0 ± 5.1186	47.8 ± 5.4086	0.1621	44.8 ± 5.6071	45.2 ± 5.9248	0.9409	0.4501
Leg Press (kg):	97.5 ± 11.0340	113.0 ± 13.8700	0.0298	75.6 ± 12.0870	95.0 ± 15.1940	0.0393	0.6429
Leg Flexion (kg):	40.5 ± 3.6684	45.4 ± 3.9703	0.1401	38.6 ± 4.0186	42.0 ± 4.3492	0.3830	0.7388
Leg Extension (kg):	47.3 ± 5.4476	50.7 ± 6.0799	0.5058	37.4 ± 5.9676	46.8 ± 6.6602	0.1237	0.3918
Mean RF Thickness (cm):	1.91 ± 0.1636	2.09 ± 0.1971	0.1173	2.00 ± 0.1336	2.06 ± 0.1825	0.2253	0.1581
Mean Quadriceps Muscle (cm):	3.40 ± 0.3984	3.79 ± 0.4737	0.2610	3.69 ± 0.2817	3.69 ± 0.3867	0.6926	0.4095

Data are mean ± SEM. RTG= Resistance Training Group, CG= Control Group, T_0= Baseline, T_1= Follow-up at 12 weeks, (W)= Within-group differences, (B)= Between-group differences, FMD= Flow-mediated Dilation, PT Isom/Lean Mass Right Leg= Peak Torque Isometric/Lean Mass Right Leg, PT Isok/Lean Mass Right Leg= Peak Torque Isokinetic/Lean Mass Right Leg, AVG Power, Isok= Average Power during the Isokinetic test, Mean RF Thickness= Mean m. Rectus Femoris Thickness.

Table 3: Overview of the number of assessments for all outcome measures.

	RTG, T_0 (n=6):	**RTG, T_1 (n=6):**	**CG, T_0 (n=9):**	**CG, T_1 (n=9):**
Diameter Rest:	6	6	4	4
Velocity Rest:	5	5	4	4
Velocity Hyperaemic:	5	5	4	4
Peak Diameter:	6	6	4	4
FMD:	6	6	4	4
PT Isom/Lean Mass Right Leg:	5	5	5	5
PT Isok/Lean Mass Right Leg:	5	5	5	5
AVG Power:	6	6	6	6
Pull Down:	6	6	5	5
Arm Press:	6	6	5	5
Shoulder Press:	6	6	5	5
Leg Press:	6	6	5	5
Leg Flexion:	6	6	5	5
Leg Extension:	6	6	5	5
Mean RF Thickness:	6	6	8	8
Mean Quadriceps Muscle:	4	4	7	7

Data are # of assessments. RTG= Resistance Training Group, CG= Control Group, T_0= Baseline, T_1= Follow-up at 12 weeks, FMD= Flow-mediated Dilation, PT Isom/Lean Mass Right Leg= Peak Torque Isometric/Lean Mass Right Leg, PT Isok/Lean Mass Right Leg= Peak Torque Isokinetic/Lean Mass Right Leg, AVG Power= Average Power, Mean RF Thickness= Mean m. Rectus Femoris Thickness.

Inschrijvingsformulier verdediging masterproef academiejaar 2020-2021,
Registration form jury Master's thesis academic year 2020-2021,

GEGEVENS STUDENT - *INFORMATION STUDENT*

Faculteit/School: **Faculteit Revalidatiewetenschappen**
Faculty/School: ***Rehabilitation Sciences***

Stamnummer + naam: **1540408 Kerkhofs Ruben**
Student number + name

Opleiding/*Programme*: **2 ma revalid. & kine musc.**

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PART A - MANDATORY - TO BE FILLED* OUT *BY THE STUDENT

Titel van Masterproef/*Title of Master's thesis:*

O behouden - *keep*

◉ wijzigen - *change to*:
Master Thesis Part 2: "What is the influence of resistance training on endothelial function in heart failure patients?"

/:

⊙ behouden - *keep*

O wijzigen - *change to*:

In geval van samenwerking tussen studenten, naam van de medestudent(en)/*In case of group work, name of fellow student(s)*:

⊙ behouden - *keep*

O wijzigen - *change to:*

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PART B - MANDATORY - TO BE FILLED OUT BY THE SUPERVISOR(S)

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☒ te verdedigen/*to defend the aforementioned Master's thesis within the aforementioned period of time*

☒ de verdediging is openbaar/*in public*

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PART C - OPTIONAL - TO BE FILLED OUT BY THE STUDENT, only if he wants to overrule part B

In tegenstelling tot het niet-bindend advies van de promotor(en) wenst de student de bovenvermelde masterproef in de bovenvermelde periode/*In contrast to the non-binding advice put forward by the supervisor(s), the student wishes:*

O niet te verdedigen/*not to defend the aforementioned Master's thesis within the aforementioned period of time*

O te verdedigen/*to defend the aforementioned Master's thesis within the aforementioned period of time*

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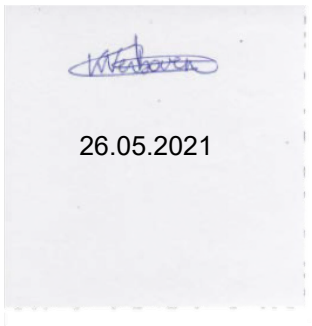
PART D - MANDATORY - TO BE FILLED OUT BY THE STUDENT AND THE SUPERVISOR(S)

Datum en handtekening student(en)
Date and signature student(s)

26.05.2021

Datum en handtekening promotor(en)
Date and signature supervisor(s)



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INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
30/09/2020	E-mail correspondentie: contactopname van student met promotor i.f.v. het verloop van MP2.	Promotor: Student:
15/10/2020	Meeting via video: het eerste overleg m.b.t. het verloop van MP2.	Promotor: Student:
17/10/2020	E-mail correspondentie: informatie omtrent de trainingsinterventie, meetmethoden en rekrutering van proefpersonen m.b.t. MP2.	Promotor: Student:
24/12/2020	E-mail correspondentie: bevraging door student van specifieke zaken die betrekking hebben op het opzet van het onderzoek.	Promotor: Student:
29/01/2021	E-mail correspondentie: eerste versie van de geschreven introductie en methode m.b.t. MP2.	Promotor: Student:
05/02/2021	E-mail correspondentie: eerste voorstel van de student tot de keuze van de uitgevoerde statistiek, i.f.v. de dataverwerking van MP2 en feedback van de introductie en methode.	Promotor: Student:
09/02/2021	E-mail correspondentie: tweede versie van de geschreven introductie en methode, inclusief doorvoering van de feedback van de promotor.	Promotor: Student:
11/02/2021	E-mail correspondentie: derde versie van de geschreven introductie met verdere verwerking van de feedback van de promotor.	Promotor: Student:
16/02/2021	E-mail correspondentie: eerste versie van het geschreven abstract en de context m.b.t. MP2.	Promotor: Student:
22/02/2021	E-mail correspondentie: doorsturen van de planning van de student m.b.t. stage en planning i.f.v. het schrijfproces. Dataset werd bevraagd.	Promotor: Student:

23/02/2021	E-mail correspondentie: ontvangst van de dataset van de promotor.	Promotor:  Student: 
24/02/2021	E-mail correspondentie: eerste versie van de verwerkte data m.b.t. de karakteristieken van de participanten voor MP2. Verdere vragen omtrent de uitkomstmaten werden geïncludeerd in deze correspondentie.	Promotor: Student: 
25/02/2021	E-mail correspondentie: eerste versie van de verwerkte data m.b.t. de *between-group differences* voor MP2.	Promotor:  Student: 
26/02/2021	E-mail correspondentie: eerste versie van de verwerkte data m.b.t. de *within-group differences* voor MP2.	Promotor: Student: 
06/05/2021	E-mail correspondentie: doorsturen van het volledige bestand door de student naar de promotor m.b.t. MP2. Respons vond plaats op 18/05/2021 inclusief feedback.	Promotor: Student: 
22/05/2021	E-mail correspondentie: tweede versie van het volledige bestand door de student naar de promotor, inclusief verwerking van feedback. Respons vond plaats op 25/05/2021 inclusief feedback.	Promotor: Student: 
26/05/2021	E-mail correspondentie: uitwisseling van documenten, benodigd voor het inschrijven en het verdedigen van MP2 in eerste zittijd.	Promotor:  Student: 

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

Naam Student(e): Ruben Kerkhofs **Datum: 2 juni 2021**

Titel Masterproef: What is the influence of Resistance Training on Endothelial Function in the Heart Failure population?

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	x	O	O
Methodologische uitwerking	O	O	O	O	x	O
Data acquisitie	x	O	O	O	O	O
Data management	O	O	O	O	x	O
Dataverwerking/Statistiek	O	O	O	x	O	O
Rapportage	O	O	O	x	O	O

2) <u>Niet-bindend advies:</u> 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)
03-06-2021	02-06-2021	

Ruben Kerkhofs <ruben.kerkhofs@student.uhasselt.be>

Inschrijvingsformulier MP2 en advies

Kenneth VERBOVEN <kenneth.verboven@uhasselt.be> 26 mei 2021 om 10:40
Aan: Ruben Kerkhofs <ruben.kerkhofs@student.uhasselt.be>

Ik verleen hierbij mijn positief (niet-bindend) advies voor het openbaar verdedigen van je masterproef op donderdag 1 juli aanstaande.

Kenneth Verboven

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Op wo 26 mei 2021 om 10:35 schreef Ruben Kerkhofs <ruben.kerkhofs@student.uhasselt.be>:
[Tekst uit oorspronkelijke bericht is verborgen]

Verklaring op Eer

Ondergetekende, student aan de Universiteit Hasselt (UHasselt), faculteit Revalidatiewetenschappen en Kinesitherapie aanvaardt de volgende voorwaarden en bepalingen van deze verklaring:

1. Ik ben ingeschreven als student aan de UHasselt in de opleiding Revalidatiewetenschappen en Kinesitherapie, waarbij ik de kans krijg om in het kader van mijn opleiding mee te werken aan onderzoek van de faculteit Revalidatiewetenschappen en Kinesitherapie aan de UHasselt. Dit onderzoek wordt beleid door Verboven Kenneth en kadert binnen het opleidingsonderdeel Wetenschappelijke Stage Deel 2. Ik zal in het kader van dit onderzoek creaties, schetsen, ontwerpen, prototypes en/of onderzoeksresultaten tot stand brengen in het domein van *"rehabilitation of internal disorders"* (hierna: "De Onderzoeksresultaten").

2. Bij de creatie van De Onderzoeksresultaten doe ik beroep op de achtergrondkennis, vertrouwelijke informatie[1], universitaire middelen en faciliteiten van UHasselt (hierna: de "Expertise").

3. Ik zal de Expertise, met inbegrip van vertrouwelijke informatie, uitsluitend aanwenden voor het uitvoeren van hogergenoemd onderzoek binnen UHasselt. Ik zal hierbij steeds de toepasselijke regelgeving, in het bijzonder de Algemene Verordening Gegevensbescherming (EU 2016-679), in acht nemen.

4. Ik zal de Expertise (i) voor geen enkele andere doelstelling gebruiken, en (ii) niet zonder voorafgaande schriftelijke toestemming van UHasselt op directe of indirecte wijze publiek maken.

5. Aangezien ik in het kader van mijn onderzoek beroep doe op de Expertise van de UHasselt, draag ik hierbij alle bestaande en toekomstige intellectuele eigendomsrechten op De Onderzoeksresultaten over aan de UHasselt. Deze overdracht omvat alle vormen van intellectuele eigendomsrechten, zoals onder meer – zonder daartoe beperkt te zijn – het auteursrecht, octrooirecht, merkenrecht, modellenrecht en knowhow. De overdracht geschiedt in de meest volledige omvang, voor de gehele wereld en voor de gehele beschermingsduur van de betrokken rechten.

6. In zoverre De Onderzoeksresultaten auteursrechtelijk beschermd zijn, omvat bovenstaande overdracht onder meer de volgende exploitatiewijzen, en dit steeds voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding:

   - het recht om De Onderzoeksresultaten vast te (laten) leggen door alle technieken en op alle dragers;
   - het recht om De Onderzoeksresultaten geheel of gedeeltelijk te (laten) reproduceren, openbaar te (laten) maken, uit te (laten) geven, te (laten) exploiteren en te (laten) verspreiden in eender welke vorm, in een onbeperkt aantal exemplaren;

[1] Vertrouwelijke informatie betekent alle informatie en data door de UHasselt meegedeeld aan de student voor de uitvoering van deze overeenkomst, inclusief alle persoonsgegevens in de zin van de Algemene Verordening Gegevensbescherming (EU 2016/679), met uitzondering van de informatie die (a) reeds algemeen bekend is; (b) reeds in het bezit was van de student voor de mededeling ervan door de UHasselt; (c) de student verkregen heeft van een derde zonder enige geheimhoudingsplicht; (d) de student onafhankelijk heeft ontwikkeld zonder gebruik te maken van de vertrouwelijke informatie van de UHasselt; (e) wettelijk of als gevolg van een rechterlijke beslissing moet worden bekendgemaakt, op voorwaarde dat de student de UHasselt hiervan schriftelijk en zo snel mogelijk op de hoogte brengt.

- het recht om De Onderzoeksresultaten te (laten) verspreiden en mee te (laten) delen aan het publiek door alle technieken met inbegrip van de kabel, de satelliet, het internet en alle vormen van computernetwerken;
- het recht De Onderzoeksresultaten geheel of gedeeltelijk te (laten) bewerken of te (laten) vertalen en het (laten) reproduceren van die bewerkingen of vertalingen;
- het recht De Onderzoeksresultaten te (laten) bewerken of (laten) wijzigen, onder meer door het reproduceren van bepaalde elementen door alle technieken en/of door het wijzigen van bepaalde parameters (zoals de kleuren en de afmetingen).

De overdracht van rechten voor deze exploitatiewijzen heeft ook betrekking op toekomstige onderzoeksresultaten tot stand gekomen tijdens het onderzoek aan UHasselt, eveneens voor de hele beschermingsduur, voor de gehele wereld en zonder vergoeding.

Ik behoud daarbij steeds het recht op naamvermelding als (mede)auteur van de betreffende Onderzoeksresultaten.

7. Ik zal alle onderzoeksdata, ideeën en uitvoeringen neerschrijven in een "laboratory notebook" en deze gegevens niet vrijgeven, tenzij met uitdrukkelijke toestemming van mijn UHasseltbegeleider(s) VERBOVEN Kenneth, HANSEN Dominique.

8. Na de eindevaluatie van mijn onderzoek aan de UHasselt zal ik alle verkregen vertrouwelijke informatie, materialen, en kopieën daarvan, die nog in mijn bezit zouden zijn, aan UHasselt terugbezorgen.

Gelezen voor akkoord en goedgekeurd,

Naam: Ruben Kerkhofs

Adres: Wolfsstraat 50, 3660 Oudsbergen

Geboortedatum en –plaats : 13/11/1997, Genk

Datum: 01/10/2020

Handtekening: