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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Response to maximal exercise in male patients with T2DM

Senne Weytjens

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

PROMOTOR :

Prof. dr. Dominique HANSEN

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2018
2019

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Acknowledgement

I dedicate this master thesis to my promoter, Prof. dr. Dominique Hansen, who I would like to thank. I appreciate his valuable time, expertise and professional guidance over the past years, and I appreciate him for trusting me with the use of his data. I would also like to thank my friends and family for their motivational support, with special thanks going to Margot Vandermoere and Stijn Vanhecke.

Dopheidestraat 31 Genk, 2 June 2019 S. W.

Research context

The current master thesis part 2 used data derived from a previous trial by Hansen D. et al., investigating optimal training modalities in patients with type 2 diabetes mellitus (T2DM). Research suggests that exercise is an effective tool in ameliorating elevated blood glucose levels (Schwingshackl, Missbach, Dias, Konig, & Hoffmann, 2014). In this study the effects of a 12-week exercise program were examined under two conditions: a group that was not allowed to eat before exercise training, trained in the fasted state, and a control group trained in the fed state. The impact of exercise training in the fasted state is a topic of intense debate, both in healthy and in diabetic patients (Haxhi, Scotto di Palumbo, & Sacchetti, 2013). Exercise training in the fasted state is presumed to stimulate mitochondrial biogenesis, improving muscle fat oxidation capacity. This could help preserve insulin sensitivity, leading to better glycaemic control.
This thesis will solely focus on the baseline measurements of this trial by Hansen D. et al., before the patients participated in a training program.

For this master thesis the central format was applied.
This thesis was a single master thesis.

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1. Abstract

Background: Type 2 diabetes mellitus (T2DM) is a systemic disease associated with reduced exercise capacity. Better comprehension of the cardiovascular, ventilatory and muscular exercise limitations underlying exercise intolerance could improve management of T2DM.

Objectives: The response to maximal exercise in male patients with T2DM was examined through maximal cardiopulmonary exercise testing (CPET). Subsequently CPET parameter of patients who exceeded their predicted VO_2peak (EPV group) and patients who remained below their predicted VO_2peak (BPV group) were compared. Parameters that significantly differed between groups were used as independent variables in a multiple regression model in order to determine predictors of %VO_2peak predicted.

Participants: Twenty-seven male patients (41 - 78 years) with T2DM were included in this study. Patients on exogenous insulin therapy were excluded. Screening affirmed absence of coronary artery disease (CAD) and congenital heart diseases based on medical history and CPET, and absence of complications of diabetes.

Measurements: During a one-day visit CPET was performed on a cycle ergometer. Dual-energy x-ray absorptiometry (DXA) scan was performed to determine body composition and a blood sample was obtained to determine the hemoglobin A1c (HbA1c) levels.

Results: The mean peak oxygen uptake capacity (VO_2peak) of the sample was 2225 ± 572 ml/min. The participants in this study had a mean VO_2peak of 98 ± 20% of their predicted value. Multiple regression analysis showed that oxygen pulse (O_2/HR) and work rate (WR) at peak exercise, which were both significantly lower in the BPV group compared to the EPV group, were significant predictors of the predicted %VO_2peak.

Conclusion: This study showed that muscular limitation was the most important contributor to exercise intolerance in this sample. Therefore exercise therapy should aim to ameliorate this muscular limitation.

Key words: type 2 diabetes mellitus, cardiopulmonary exercise testing

2. Introduction

In 2014, diabetes mellitus (DM) affected an estimated 422 million adults worldwide (Collaboration, 2016). Patients with type 2 diabetes mellitus (T2DM), in the absence of cardiovascular complications, have a decreased exercise capacity. Peak oxygen uptake (VO_2peak) is reduced by approximately 20% compared to healthy subjects matched for age and physical activity level (Regensteiner, Sippel, McFarling, Wolfel, & Hiatt, 1995). Reduced exercise capacity is a strong predictor of cardiovascular disease and all-cause mortality (Wei et al., 1999). Cardiovascular disease is the most common complication of diabetes (Gleissner, Galkina, Nadler, & Ley, 2007; Laakso, 1999), and cardiovascular mortality is two to four times higher in diabetic patients compared to non-diabetic patients (Belke & Dillmann, 2004; Grundy et al., 1999). Understanding mechanisms associated with reduced exercise capacity in T2DM is important, since they may precede the development of cardiovascular complications commonly associated with more advanced DM. Mechanisms associated with reduced exercise capacity in T2DM have not been fully elucidated. Diabetes is a systemic disease, meaning that it can affect almost every organ in the body, potentially affecting cardiovascular performance, pulmonary gas exchange and skeletal muscle function, the three determinants of exercise capacity. Certain mechanisms causing exercise intolerance have already been described.

Resting heart rate (HR) is slightly higher and peak HR is slightly reduced in patients with T2DM compared to healthy controls, resulting in a reduced heart rate reserve (HRR) (Green, Egana, Baldi, Lamberts, & Regensteiner, 2015; Lalande, Hofman, & Baldi, 2010). Cardiovascular autonomic neuropathy (CAN), a potential complication of DM, reduces response in HR during exercise (Kahn, Zola, Juni, & Vinik, 1986). CAN encompasses damage to the autonomic nerve fibers of the vagal nerve that innervate the heart, causing a fixed, unresponsive heart rate in the final phase, thus impairing exercise capacity (Vinik & Ziegler, 2007). There is no strong evidence that peak stroke volume (SV) is reduced in T2DM (Gusso et al., 2008; Regensteiner et al., 2009). Collectively these findings suggest that peak cardiac output (CO) may be reduced in patients with T2DM. Several studies show a reduction in CO of five to ten percent compared to control subjects, though differences were not statistically significant (Baldi, Aoina, Oxenham, Bagg, & Doughty, 2003; Regensteiner et al., 2009). End-diastolic volume (EDV), a measure of the filling of the ventricle, is decreased in patients with

T2DM compared to control subjects. At rest this is compensated by an increased ventricular contractility, lowering the end-systolic volume (ESV) and normalizing SV. During exercise this systolic compensation is no longer observed: ESV decreases less in patients with T2DM, indicating reduced contractile reserve (Pinto et al., 2014). Diabetic patients are at risk of developing diabetic cardiomyopathy (DCM) (Fein & Sonnenblick, 1994). This complication of DM causes diastolic or systolic cardiac dysfunction in diabetic patients without other obvious causes of cardiomyopathy, such as coronary artery disease (CAD), hypertension, or valvular heart disease (Schilling & Mann, 2012). DCM results from the structural, functional and regulatory remodeling of the heart induced by DM, affecting cardiac function. Left ventricular dysfunction also contributes to lower exercise capacity in patients with T2DM (Poirier et al., 2000). Other research shows that the total blood volume in men with T2DM is reduced compared to healthy men matched for age, weight and physical activity level, and this is correlated with a lower EDV (Lalande et al., 2010).

Pulmonary function also appears to be reduced in patients with T2DM. Spirometry demonstrates that forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), vital capacity (VC) and peak expiratory flow (PEF) are lower than predicted values derived from age, gender and height-matched healthy population data. A linear regression model shows that diabetes duration has a stronger influence than glycaemic control (Davis, Knuiman, Kendall, Vu, & Davis, 2000). A 15-year follow-up study also found reduced FVC and FEV_1 in patients with T2DM, but concludes deterioration is not progressive in the long term, and instead only occurs during early stages of DM (Lange, Parner, Schnohr, & Jensen, 2002). Conflicting evidence has been found regarding diffusion capacity. Decreased diffusion capacity of the lung for carbon monoxide (DLCO) compared to predicted values is reported in a study of nonsmoking patients with T2DM (Guazzi, Oreglia, & Guazzi, 2002), but these findings are contradicted by other studies (Ozmen et al., 2002; Ozsahin, Tugrul, Mert, Yuksel, & Tugrul, 2006).

Several studies demonstrate patients with T2DM have reduced muscle strength in the lower extremities compared to controls, and preserved muscle strength in the upper extremities (Andersen, Nielsen, Mogensen, & Jakobsen, 2004; Orlando, Balducci, Bazzucchi, Pugliese, & Sacchetti, 2017). Furthermore muscle dysfunction in T2DM is characterized by increased fatigability affecting both upper and lower extremities (Orlando et al., 2017). Various components are presumed to contribute to this skeletal muscle dysfunction.

Regression analysis shows that peripheral neuropathy, a common complication of diabetes, is related to muscle weakness (Andersen et al., 2004). Changes have been found in the muscle tissue of patients with T2DM: there is a significant smaller proportion of slow oxidative fibers and a significant larger proportion of fast glycolytic fibers. These changes in fiber type composition contribute to a reduced oxidative capacity and increased glycolytic capacity of skeletal muscles of patients with T2DM (Oberbach et al., 2006). Furthermore GLUT4 density is significantly lower in slow oxidative fibers of patients with T2DM (Gaster, Staehr, Beck-Nielsen, Schroder, & Handberg, 2001), and skeletal muscle mitochondria are smaller and have reduced activity in obese patients with T2DM (Kelley, He, Menshikova, & Ritov, 2002). A significantly lower arteriovenous O_2 difference in patients with T2DM compared to healthy controls may indicate a reduced skeletal muscle O_2 extraction, but further research will have to elucidate this (Baldi et al., 2003).

This master thesis will elaborate on the mechanisms leading to exercise intolerance in male patients with T2DM. The present study aimed to explore the response to maximal exercise in male patients with T2DM using maximal cardiopulmonary exercise testing (CPET). Better comprehension of exercise limiting factors in T2DM could lead to improvements in the management of this chronic disease. Furthermore CPET parameter of patients who exceeded their predicted VO_2peak (EPV group) and patients who remained below their predicted VO_2peak (BPV group) were compared. Parameters that significantly differed between groups were used as independent variables in a multiple regression model in order to determine predictors of %VO_2peak predicted.

3. Methods

3.1. Research design

An exploratory cross-sectional study was used to investigate the research questions.

Patients were screened, in advance of their consultation, for following elements: diagnosis of T2DM, medication, absence of CAD and congenital heart diseases based on medical history and CPET and absence of complications of DM. All subjects had to sign and hand in the informed consent documents before participating in the study. During a one-day visit, patients performed a maximal CPET and received a DXA scan. A blood sample was obtained to determine the hemoglobin A1c (HbA1c) levels.

This thesis evaluated the response to maximal exercise in male patients with T2DM using maximal cardiopulmonary exercise testing (CPET). Since there was no control group, the outcome measures were compared to predicted values and reference values. Subsequently the data of the participants were divided into two groups, the first group consisting of data of patients who exceeded their predicted VO_2peak (EPV group), and the second group consisting of data of patients who remained below their predicted VO_2peak (BPV group). Then these two groups were compared to speculate which parameters are affected in patients with reduced exercise capacity. Parameters that significantly differed between groups were used as independent variables in a multiple regression model in order to determine predictors of %VO_2peak predicted.

All CPET and DXA scan results discussed in this thesis were derived from a previous trial by Hansen D. et al. investigating the effects of exercise (12-week exercise program) in the fasted state in male patients with T2DM, and date from 2014. Data of this study were handed to me by my promoter, Prof. Dr. Dominique Hansen. The aforementioned study has not been published, therefore it is not possible to reference to this study.

3.2. Participants

A total of 27 male patients (41 - 78 years) were included in this study. They all met the American Diabetes Association diagnostic criteria for T2DM (HbA1c ≥6.5% or fasting blood

glucose (FBG) ≥126 mg/dL) (Chamberlain, Rhinehart, Shaefer, & Neuman, 2016). Only patients on oral anti-diabetic drugs were allowed to participate, patients on exogenous insulin therapy were excluded, and medical treatment had to be stable for at least three months before inclusion. All participants had permission of a physician to perform a maximal exercise test. Included patients performed less than two hours of physical activity per week, and were not on a diet. Cardiovascular disease (previous cardiac surgery and/or cardiac arrest), pulmonary disease, kidney disease and significant orthopedic disorders were ruled out before inclusion in this study. Simultaneous participation in another clinical trial was not allowed. Patient characteristics are displayed in table 1. Patients were recruited through several channels: at the Jessa hospital (Hasselt, Belgium), through an advertisement on the website of the Flemish Diabetes Association ("Vlaamse Diabetes Liga"), via general practitioners in the area of Hasselt, Belgium and via the senior university of Hasselt.

3.3. CPET

3.3.1. Protocol

Subjects performed a maximal CPET on a cycle ergometer (eBike Basic, General Electric GmbH, Bitz, Germany) with pulmonary gas exchange analysis (Jaeger Oxycon, Erich Jaeger GmbH, Germany). CPET is the gold standard in exercise capacity evaluation. Jaeger calibration (ambient conditions, volume calibration and O2/CO2 calibration) was performed before every exercise testing and leakages of the breathing mask were checked in order to secure reliability and validity of the measurements. Peak oxygen uptake capacity (VO_2peak) and maximal workload capacity (Wpeak) were determined by an exhaustive incremental exercise test using a one-minute work stage protocol with a starting workload of 40W and increments of 20W every minute. Measurements of expired gases were performed continuously. 12-lead electrocardiogram continuously monitored heart rate and rhythm. The benchmark for a successful maximal CPET was a respiratory exchange ratio (RER) ≥ 1.10 in combination with dyspnea, leg and/or general fatigue. Subjects were encouraged to cycle until exhaustion. The CPET was ended when patients were no longer able to maintain a cycling frequency of 55 rpm or higher.

3.3.2. Data collection

First the respiratory exchange ratio (RER) and maximal heart rate (HR) were evaluated to ensure that all participants achieved maximal exertion, and to exclude motivation as a potential exercise limiting factor. Motivational limitation was defined as a maximal RER <1.10 or a maximal HR < 85% of predicted maximal HR, except for patients treated with beta blockers (American Thoracic & American College of Chest, 2003).

In order to examine exercise limiting factors in T2DM, various outcome measures were derived from the maximal CPET for statistical analysis. Oxygen uptake (VO_2), carbon dioxide release (VCO_2) and minute ventilation (V'E) were directly measured by the Oxycon breath-by-breath system during exercise testing, other parameters were calculated by the computer.

VO_2peak (ml/min) is the highest O_2 uptake obtained during exercise and is influenced by cardiovascular, pulmonary and skeletal muscle function. The VO_2 reaches a plateau phase, despite work rate continuing to increase. Predicted VO_2peak was calculated by a formula established in previous research (Hansen, Sue, & Wasserman, 1984). RER is defined as the VCO_2/VO_2 ratio. As exercise progresses to higher intensities, VCO_2 surpasses VO_2, and the ratio will increase. The RER indicates the fuels used for metabolism. RER of 1 suggests carbohydrates; RER of 0.7 lipids and RER of 0.85 a mixture of carbohydrates and lipids. A RER above 1.1 is considered a criterion to define a maximal exercise test.

Peak heart rate (HRpeak) (min^{-1}) determines the upper limit of the cardiovascular capabilities during physical activity. In healthy subjects, HR increases quasi-linearly with increasing VO_2. HRpeak diminishes with aging, which contributes to decreases in exercise capacity with aging. Oxygen pulse (O_2/HR) (ml O_2/beat) reflects the stroke volume response to exercise.

V'E (l/min) progressively increases during incremental exercise testing; primarily tidal volume will increase and - as exercise progresses - breathing frequency will also start increasing. Breathing reserve (BR) (%), expresses as the difference between the maximal voluntary ventilation (MVV) and the maximum V'E as a fraction of the MVV, should remain above 20%, even during maximal exercise (Balady et al., 2010). Tidal volume at maximal exercise (Vtmax) (l) was defined as the V'E at maximal exercise (V'Emax) divided by the breathing frequency at maximal exercise (BFmax). The lowest V'E/VO_2 ratio and lowest

$V'E/VCO_2$ ratio during exercise are both noninvasive measurements of ventilatory efficiency. Predicted values for lowest VE/VCO_2 were calculated by a formula established in previous research (Sun, Hansen, Garatachea, Storer, & Wasserman, 2002).

Work rate (WR) at maximal exercise was compared to predicted values calculated by a formula established in previous research (Van de Poppe, Hulzebos, Takken, & Low-Land Fitness Registry Study, 2018). The first ventilatory threshold (VT1) was determined using the V-slope method (Beaver, Wasserman, & Whipp, 1986). It demarcates the upper limit of exercise intensity that can be attained almost entirely aerobically. The second ventilatory threshold (VT2) was determined by plotting V'E against VCO_2 (Beaver et al., 1986). The break point indicates the onset of relative hyperventilation: V'E rises more rapidly than VCO_2. The rate at which VO_2 increased per work rate ($\Delta VO_2/\Delta WR$) (ml/min/W), was calculated as an indicator of aerobic efficiency. Low values indicate poor oxygen uptake kinetics, which may be due the several pathological conditions (Nichols et al., 2018).

For all outcome measures the value at VO_2peak, predicted maximal value and %predicted maximal value were collected.

Body fat percentage (BFP) was derived from the DXA scan results. The DXA scan used X-radiation to measure bone mineral density and body composition (fat mass and lean tissue mass). Dual X-ray absorptiometry is considered the gold standard measurement of body composition. A blood sample was obtained to determine the HbA1c levels.

Medication was also taken into account. Diabetes medications were divided into five groups, all influencing blood glucose levels differently. Metformin improves insulin sensitivity. Glinides and sulfonylureas promote the release of insulin from the pancreas. Inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors) increase incretin levels, which inhibit glucagon release and in turn increases insulin secretion. Glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) are agonists of the GLP-1 receptor, and cause increased insulin secretion.

3.4. Ethical approval

The trial by Hansen D. et al., labeled the ExTiDi study, was approved in July 2013 by the Ethics Committee of the Jessa Hospital (Hasselt, Belgium) and the Medical Ethics Committee of UHasselt (Diepenbeek, Belgium).

3.5. Data analysis

JMP Pro 14.1.0 software was used for statistical analysis.
Patient characteristics of the sample (n=27) were portrayed as mean ± standard deviation for continuous data, and as frequency and percentage for categorical variables. Shapiro-Wilk test was used to test normality of continuous data.

Comparison of within-group differences (measurements at VO2peak versus predicted maximal values): Before CPET parameter values at VO_2peak were compared to predicted maximal values, assumption of normality was tested with Shapiro-Wilk test. Wilcoxon signed-rank test was used to compare means of these two dependent samples of data, due to the small sample size (n=27).

The sample then was divides into two groups, the EPV group (n=13) and the BPV group (n=14). Assumptions of normality and homoscedasticity were evaluated for continuous data of patient characteristics of both groups. Comparison of continuous data from baseline characteristics was performed by Mann-Whitney U test. Frequency distribution of categorical data, was compared with a chi-square test (when expected cell counts were greater than or equal to five) or Fisher's exact test.
Comparison of between-group differences (EPV group versus BPV group): Before CPET parameter values at VO_2peak were compared between both groups, assumptions of normality and homoscedasticity were tested. Mann-Whitney U test was used to compare means of these two independent samples of data, due to the small sample sizes.

Determining significant predictors of %VO_2peak predicted in male patients with T2DM: Residual plots were examined to evaluate assumptions for multiple linear regression: a linear relationship between %VO_2peak predicted and the independent variables, normal distribution of residuals, and homoscedasticity of residuals. All CPET parameters that were significantly different between the EPV group and BPV group were included as independent variables in this regression model.

4. Results

4.1. Characteristics

A total of 27 male patients with T2DM were included in this thesis. The characteristics of these subjects can be found in table 1. All continuous data were normally distributed, except for HbA1c (%). The patients were divided into two groups based on their VO_2peak: one group of subjects that exceeded their predicted VO_2peak (EPV group, n=13) and another group of subjects that remained below their predicted VO_2peak (BPV group, n=14). Again all characteristics were normally distributed, except for HbA1c (%). The majority of participant had a HbA1c between six and seven %, but outliers were only found to the right of this peak, which can be expected in a diabetic population. Comparison between the EPV group and BPV group showed no significant differences, except for body mass index (BMI) (kg/m^2), which was significantly lower in the EPV group.

4.2. Response to maximal exercise

In table 2 the results of the CPET are displayed. A total of 27 participants performed a maximal exercise test. First the respiratory exchange ratio (RER) and maximal heart rate (HR) were evaluated to ensure that all participants achieved maximal exertion. All participants reached a RER > 1.10, and 23 participants (85%) reached a maximal HR >85% of the predicted maximal HR.

The mean VO_2peak for this sample was 2225 ± 572 ml/min. This corresponds to 98 ± 20% of the predicted value. There was no significant difference between the mean VO_2peak and the predicted VO_2peak (2275 ± 359 ml/min, p = 0.5114). The mean respiratory exchange ratio (RER) at VO_2peak was 1.20 ± 0.09.

The mean HR at VO_2peak (HRpeak) was 149 ± 21 min^{-1}, which corresponds to 94 ± 10% of the predicted value. There was a significant difference between the mean HRpeak and the predicted HR at VO_2peak (158 ± 9 min^{-1}, p = 0.0057). Mean oxygen pulse (O_2/HR) at VO_2peak was 16.1 ± 3.3 ml O_2/beat, which corresponds to 100 ± 28.% of the predicted value. There

was no significant difference between the mean O_2 pulse at VO_2peak and the predicted O_2 pulse at VO_2peak (16.2 ± 3.0 ml O_2/beat, p = 0.8243).

The mean ventilation at VO_2peak (V'Emax) was 87 ± 21 l/min, which corresponds to 89 ± 17% of the predicted value. There was a significant difference between the mean ventilation at VO_2peak and the predicted ventilation at VO_2peak (97 ± 13 l/min, p = 0.0007). The mean breathing reserve (BR) at VO_2peak was 35 ± 12%, which corresponds to 131 ± 47% of the predicted value. There was a significant difference between the mean BR at VO_2peak and the predicted BR at VO_2peak (27 ± 1%, p = 0.0009). The mean tidal volume at VO_2peak (Vtmax) was 2.94 ± 0.96 l. The mean lowest V'E/VO_2 ratio was 25.01 ± 3.59 and the mean lowest V'E/VCO_2 ratio was 27.75 ± 3.27.

The mean work rate at VO_2peak (WRmax) was 181 ± 48 W, which corresponds to 73 ± 20% of the predicted value. There was a significant difference between the mean WRmax and the predicted WR at VO_2peak (250 ± 40W, p < 0.0001). On average, the first ventilatory threshold (VT1) occurred at 1151 ± 306 mlO_2/min, which corresponds with 53 ± 11% of VO_2peak, and the second ventilatory threshold (VT2) occurred at 2017 ± 500 mlO_2/min, which corresponds with 87 ± 6% of VO_2peak. Only 18 participants (67%) reached their VT2 during maximal exercise testing. The mean rate at which VO_2 increased per work rate ($\Delta VO_2/\Delta WR$) was 12.8 ± 1.9 ml/min/W.

4.3. Comparison between EPV group and BPV group

In table 3 the CPET results of the EPV group and BPV group are displayed. The mean VO_2peak was significantly higher in the EPV group (2581 ± 490ml/min) compared to BPV group (1894 ± 434 ml/min) (p = 0.0015). Percentage of predicted VO_2peak was also significantly higher in the EPV group (113 ± 16%) compared to the BPV group (84 ± 13%) (p < 0.0001).

CPET parameters that significantly differed between groups were presumed to be potential predictors of exercise capacity. Mean oxygen pulse (O_2/HR) at VO_2peak was significantly higher in the EPV group (17.9 ± 2.9 mlO_2/beat) compared to BPV group (14.5 ± 2.7 mlO_2/beat) (p = 0.0048). The mean WR at VO_2peak (WRmax) was significantly higher in the EPV group (211 ± 44 W) compared to BPV group (153 ± 33 W) (p = 0.0018). VT1 and VT2

(mlO_2/min) were also significantly higher in the EPV group compared to the BPV group (p = 0.0186 and p = 0.0145 respectively).

RER, HRpeak, V'Emax, BR at VO_2peak, Vtmax, lowest V'E/VO_2, lowest V'E/VCO_2, relative ventilatory thresholds and $\Delta VO_2/\Delta WR$ were not significantly different between groups.

4.4. Determining predictors of %VO_2peak predicted in male patients with T2DM

After comparing EPV group and BPV group, it appears exercise intolerance is not due to pulmonary limitations in this sample. Significant between-group differences were found for O_2/HR (mlO_2/beat), WRmax (W), VT1 (ml/min) and VT2 (ml/min), suggesting potential cardiovascular and muscular limitations. These four CPET parameters were included as independent variables in a multiple linear regression model as potential predictors of %VO_2peak predicted.

A multiple linear regression model of estimated mediators of VO_2peak showed that O_2/HR and WRmax were significant variables in explaining lower % VO_2peak predicted (Table 4). VT1 and VT2 were not significant predictors for this regression model. The adjusted R-squared showed that 76% of the variation in the data is accounted for by the regression model, and the F-test indicated that the regression model provided a better fit to the data than a model that contains no independent variables (p = 0.0001).

5. Discussion

Multiple regression analysis showed that O_2/HR and WR at peak exercise, which were both significantly lower in the BPV group compared to the EPV group, were significant predictors of the predicted %VO_2peak in this sample (n=27) of male patients with T2DM.

5.1. Interpretation of CPET parameters

VO_2peak is a parameter used to express cardiorespiratory fitness. According to the American Thoracic Society, VO_2peak should be >84% of the predicted value to be considered normal (American Thoracic & American College of Chest, 2003). The sample in this master thesis had a VO_2peak of 98 ± 20% of their predicted value. Four participants (15%) did not reach a VO_2peak >84% of their respective predicted VO_2peak value, indicating the presence of exercise intolerance.

Other parameters have to be evaluated in order to determine which system caused the exercise limitation and to understand underlying pathophysiology, although the mean VO_2peak of the participants of this study did not suggest decreased cardiorespiratory fitness. These results are not in accordance with previous research stating patients with T2DM, in the absence of cardiovascular complications, have a decreased exercise capacity compared to healthy subjects matched for age and physical activity level (Regensteiner et al., 1995). A possible explanation for this could be that only more physically fit patients with T2DM were motivated to participate in a study with a 12-week exercise program (all participants attended in a 12-week exercise program during the ExTiDi study; in this master thesis only baseline measurements of this study are discussed). Another possible explanation of the quasi-normal VO_2peak found in this thesis is the fact all participants were male. Previous research suggest that women with T2DM may have a greater exercise impairment than their male counterparts compared with healthy controls matched for gender and age (Regensteiner et al., 1995).

HR at VO_2peak and O_2 pulse at VO_2peak are cardiovascular parameters. According to the American Thoracic Society, HRpeak should reach >90% of the predicted value to be considered normal (American Thoracic & American College of Chest, 2003). The sample in

this master thesis had a HRpeak of 94 ± 10% of their predicted value. Nine participants (33%) did not reach a HRpeak >90% of their respective predicted HRpeak value, which might indicate that these participants had to terminate the exercise test before reaching their cardiac limitation, or might be an indicator of insufficient chronotropic response of the heart to physical activity. Insufficient chronotropic response could be due to external factors, for example the use of beta blockers (one participant confirmed using a beta blocker), or due to internal factors, for example cardiovascular autonomic neuropathy (CAN), a potential complication of diabetes mellitus (Vinik & Ziegler, 2007).

According to the American Thoracic Society, O_2 pulse (O_2/HR) should reach >80% of the predicted value to be considered normal (American Thoracic & American College of Chest, 2003). The sample in this master thesis reached an O_2/HR of 100 ± 28% of their predicted value. Six participants (22%) did not reach an O_2/HR >80% of their respective predicted O_2/HR value at VO_2peak, which might indicate that these participants had to terminate the exercise test before reaching their cardiac limitation, or might indicate that the heart is unable to adequately increase the O_2/HR. Insufficient inotropic response could be due to external factors, for example the use of calcium antagonists (four participants confirmed using calcium antagonists), or due to internal factors causing reduced stroke volume response to exercise. Blunted exercise stroke volume response has already been determined in female adolescents with T2DM (Gusso et al., 2008), but there is no strong evidence that insufficient inotropic response of the heart to exercise is caused by complications of T2DM.

Breathing reserve (BR%) at VO_2peak is a respiratory parameter. BR% at VO_2peak should be >20% to be considered normal (Balady et al., 2010). At peak exercise the sample in this master thesis had a BR% of 35 ± 12%. Two participants (7%) had a breathing reserve <20% at peak exercise, which might indicate that these participants had to terminate the exercise test due to a ventilatory exercise limiting factor. Breathing reserve depends on two main factors: ventilatory demand and ventilatory capacity. Ventilatory demand is affected by metabolic demand and body weight. Ventilatory capacity is influenced by mechanical factors such as airflow limitation and operating lung volumes, ventilatory muscle function, genetic endowment, aging, and disease (Johnson, Weisman, Zeballos, & Beck, 1999). Thus T2DM, a condition often seen in combination with obesity, which is associated with a restrictive lung ventilatory defect (Nakajima et al., 2008), could potentially cause patients with T2DM to terminate the exercise test due to a ventilatory exercise limiting factor.

WRmax is a muscular parameter. The sample in this master thesis had a WRmax of 73 ± 20% of their predicted value. This might indicate a muscular exercise limiting factor. Previous research demonstrated patients with T2DM have reduced muscle strength and increased fatigability in the lower extremities compared to controls (Orlando et al., 2017). Peripheral neuropathy (Andersen et al., 2004), shifted muscle fiber type proportions (Oberbach et al., 2006) and mitochondrial dysfunction (Kelley et al., 2002) may contribute to this muscular limitation. $\Delta VO_2/\Delta WR$ represents the ability of exercising muscle to extract oxygen. The lowest limit for normal value of ΔVO2/ΔWR is 8.6 ml/min/W (Herdy et al., 2016). The mean $\Delta VO_2/\Delta WR$ in this sample was 12.8 ± 1.9 ml/min/W. One participant (4%) did not reach a $\Delta VO_2/\Delta WR$ >8.6 ml/min/W. $\Delta VO_2/\Delta WR$ does not reflect the efficiency of muscle contraction, which might be affected considering the reduced WRmax. Reduced efficiency of muscle contraction might be due to shifted muscle fiber type proportions: there is a significant smaller proportion of slow oxidative fibers and a significant larger proportion of fast glycolytic fibers in patients with T2DM (Oberbach et al., 2006). Muscle fiber type proportions were not taken into account in this study.

5.2. Comparison between EPV group and BPV group

Significant differences were found in VO_2peak (ml/min) and VO_2peak (%predicted) between the EPV group and the BPV group (table 3). This was expected since group assignment was based on the percentage of the predicted value of VO_2peak. Mean predicted VO_2peak values were not significantly different between groups.

Significant between-group differences were found for O_2/HR (mlO_2/beat), WRmax (W), VT1 (ml/min) and VT2 (ml/min). These parameters were presumed to be potential predictors of exercise capacity. Relative ventilatory thresholds were not significantly different between groups. This might be explained by the significant difference in VO_2peak between groups.

None of the pulmonary CPET parameters (V'Emax, BR%, Vtmax, lowest $V'E/VO_2$ and lowest $V'E/VCO_2$) were significantly different between groups. This indicates exercise intolerance was not determined by a ventilatory limitation in this sample.

5.3. Predictors of VO_2peak

In a study of 39 sedentary patients with T2DM between age 40 and 70, multivariable regression analysis, after adjusting for age and gender, showed that higher high-density lipoprotein (HDL) cholesterol ($p = 0.022$), lower sagittal abdominal diameter ($p = 0.001$) and lower skeletal muscle fat content ($p = 0.046$) were significant predictors of VO_2peak (Bacchi et al., 2014). Other research concerning 39 male patients with T2DM aged 66 ± 2 years, found significantly lower insulin sensitivity and significantly reduced number of type 1 muscle fibers compared to subjects with impaired glucose tolerance and normal glucose tolerance matched for age, weight and BMI. Multiple regression analysis showed that insulin sensitivity and muscle fiber distribution were significant predictors of VO_2peak ($p <0.001$) (Segerstrom et al., 2011). No previous research assessed the role CPET parameters in predicting VO_2peak through regression analysis. The purpose of this study was to indentify predictors of exercise intolerance in a sample of male patients with T2DM. The percentage of VO_2peak predicted was used as dependent variable in the multiple regression model, instead of VO_2peak (ml/min), since this parameter is corrected for age, gender, weight and height.

Body composition (DXA scan), medication and CPET parameters were all taken into account. However, after comparing the EPV group to the BPV group, body composition and medication (table 1), as well as ventilatory CPET parameters (table 3) were excluded as potential predictors of exercise intolerance.

Multiple linear regression showed that O_2/HR and WRmax were significant variables in explaining lower % VO_2peak predicted (Table 4). However, O_2/HR was not reduced in this overall sample (table 2). The results indicate that exercise therapy, a cornerstone in the management of T2DM, should aim on ameliorating muscular deficits of patients in this sample. Reduced exercise capacity is a strong predictor of cardiovascular disease, which is the leading cause of mortality in patients with T2DM (Belke & Dillmann, 2004; Wei et al., 1999).

Previous research compared the results of a six-month training program in patients with T2DM. 251 subjects between age 39 and 70 were randomized over four groups with different exercise interventions: aerobic exercise training, resistance exercise training, the combination of aerobic and resistance exercise training and a control group. Baseline CPET

results were compared to results after six months. WRmax was significantly higher in the aerobic training group and the combined exercise group compared with the resistance training group and the control group. Combined aerobic and resistance training did not result in significantly higher WRmax compared with aerobic training alone (Larose et al., 2010). Aerobic training alone appears to be sufficient for ameliorating the muscular limitation observed in the sample of this master thesis.

Future research concerning optimal exercise prescriptions in T2DM will be necessary.

5.4. Critical appraisal of the master thesis

The mean VO_2peak of the patients with T2DM in this master thesis was not significantly lower than predicted VO_2peak values. This might imply that most of the participants in this study had a relatively normal physical activity level (with only four participants not reaching a VO2peak >84% of their respective predicted VO2peak value). Therefore the sample in this thesis might not be a good representation of the total population of patients with T2DM meeting the inclusion criteria, since previous research demonstrated a reduced exercise capacity in patients with T2DM (Regensteiner et al., 1995).

Small sample size was a limitation of this thesis. The study therefore also had lower statistical power. The power of regression analysis is determined by sample size (increasing sample size would increase power) and the amount of independent variables (increasing amount of predictors would decrease power).

The prediction equation for WRmax used in this thesis was developed by analyzing CPET results of subjects between age 20 and 60 (Van de Poppe et al., 2018). This might be a limitation, since the patients in the current study were between age 41 and 78, and had a WRmax of 73 ± 20% of their predicted value. The prediction equation potentially was not adequate for this sample. However, simple linear regression showed that age was not a significant predictor of %WRmax predicted. Therefore it was concluded that - if the prediction equation overestimated the participants - older participants were not disadvantaged by the prediction equation.

6. Conclusion

This study showed that O_2/HR and WR at peak exercise were significant predictors of the predicted %VO_2peak in this sample (n=27) of male patients with T2DM. Overall, muscular limitation appears to be the most important contributor to exercise intolerance in this sample. Therefore exercise therapy should aim to ameliorate this muscular limitation. Future research concerning optimal exercise prescriptions to accomplish this purpose will be necessary.

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8. Appendices

Table 1. Patient characteristics

	TOTAL (N=27)	EPV group (N=13)	BPV group (N=14)	p-value
Age (years)	61.8 ± 8.7	59.9 ±9.7	63.6 ± 7.5	0.2431
BMI (kg/m^2)	29.74 ± 4.2	28.22 ± 4.2	31.16 ± 3.7	0.0392*
HbA1c (%)	7.39 ± 1.4	7.08 ± 1.0	7.68 ± 1.6	0.2202
Smoker (Yes)	5 (19%)	1 (8%)	4 (29%)	0.3304
Height (cm)	177 ± 7	177 ± 6	177 ± 8	0.9227
Weight (kg)	93 ± 15	88 ± 15	98 ± 14	0.1203
Body fat percentage (%)	32.01 ± 4.8	30.45 ± 4.9	33.46 ± 4.4	0.1384
Lean tissue mass (%)	68.0 ± 4.8	69.6 ± 4.9	66.5 ± 4.4	0.1384
Diabetes medication:				
– **Metformin**	24 (89%)	10 (77%)	14 (100%)	0.0978
– **Glinides**	3 (11%)	0 (0%)	3 (21%)	0.2222
– **Sulfonylureas**	8 (30%)	4 (31%)	4 (29%)	1.0000
– **DPP-4 inhibitors**	9 (33%)	4 (31%)	5 (36%)	1.0000
– **GLP-1 receptor agonists**	3 (11%)	1 (8%)	2 (14%)	1.0000
Statins	15 (56%)	6 (46%)	9 (64%)	0.3434
Antiplatelet drugs	12 (44%)	5 (38%)	7 (50%)	0.5466
Antihypertensive drugs:				
– **Calcium antagonists**	4 (15%)	1 (8%)	3 (21%)	0.5956
– **Diuretics**	3 (11%)	2 (15%)	1 (7%)	0.5956
– **ACE inhibitors**	8 (30%)	2 (15%)	6 (43%)	0.2087
– **angiotensin II receptor antagonists**	5 (19%)	3 (23%)	2 (14%)	0.6483
– **Beta blockers**	1 (4%)	0 (0%)	1 (7%)	1.0000
Bronchodilators	1 (4%)	0 (0%)	1 (7%)	1.0000

*(Continuous variables: mean ± SD; Qualitative variables: frequency and percentage. * : significant difference (p<0.05) between EPV group and BPV group. Smoker (yes): participant was a smoker during data collection.)*

Table 2.

CPET parameters	Sample (N=27)	Predicted value	p-value	% predicted
VO_2peak (ml/min)	2225 ± 572	2275 ± 359	0.5114	98 ± 20
RER	1.20 ± 0.09	-	-	-
HRpeak (min^{-1})	149 ± 21	158 ± 9	0.0057*	94 ± 10
O_2/HR (ml O_2/beat)	16.1 ± 3.3	16.2 ± 3.0	0.8243	100 ± 28.0
V'Emax (l/min)	87 ± 21	97 ± 13	0.0007*	89 ± 17
BR (%)	35 ± 12	27 ± 1	0.0009*	131 ± 47
Vtmax (l)	2.94 ± 0.96	-	-	-
Lowest V'E/VO_2	25.01 ± 3.59	-	-	-
Lowest V'E/VCO_2	27.75 ± 3.27	27.96 ± 1.06	0.6909	99 ± 11
WRmax	181 ± 48	250 ± 40	<0.0001*	73 ± 20
VT1 (mlO_2/min)	1151 ± 306	-	-	-
VT1 (%)	53 ± 11	-	-	-
VT2 (mlO_2/min)†	2017 ± 500	-	-	-
VT2 (%)†	87 ± 6	-	-	-
ΔVO_2/ΔWR (ml/min/W)	12.8 ± 1.9	-	-	-

*(All variables are presented as mean ± SD. * : significant difference (p<0.05) between value at VO_2peak and predicted maximal value. †: N=18. VO_2peak: peak oxygen uptake, HRpeak: heart rate at VO_2peak, O_2/HR: oxygen pulse at VO_2peak, V'Emax: ventilation at VO_2peak, BR: breathing reserve at VO_2peak, Vtmax: tidal volume at VO_2peak, WRmax: work rate at VO_2peak.)*

Table 3.

CPET parameters	EPV group (N=13)	BPV group (N=14)	p-value
VO_2peak (ml/min)	2581 ± 490	1894 ± 434	0.0015*
% VO_2peak predicted	113 ± 16	84 ± 13	<0.0001*
RER	1.18 ± 0.06	1.22 ± 0.12	0.7138
HRpeak (min^{-1})	158 ± 15	141 ± 22	0.0551
O_2/HR (ml O_2/beat)	17.9 ± 2.9	14.5 ± 2.7	0.0048*
V'Emax (l/min)	95 ± 18	79 ± 20	0.0804
BR (%)	30 ± 11	40 ± 12	0.0549
Vtmax	3.08 ± 1.03	2.82 ± 0.92	0.7896
Lowest V'E/VO_2	23.95 ± 3.14	25.99 ± 3.81	0.1148
Lowest V'E/VCO_2	26.72 ± 2.89	28.71 ± 3.41	0.1523
WRmax	211 ± 44	153 ± 33	0.0018*
VT1 (mlO_2/min)	1297 ± 299	1016 ± 253	0.0186*
VT1 (%)	51 ± 10	55 ± 12	0.3198
VT2 (mlO_2/min)†	2347 ± 452	1753 ± 372	0.0145*
VT2 (%)†	87 ± 8	86 ± 5	0.9646
ΔVO_2/ΔWR (ml/min/W)	12.7 ± 2.0	12.9 ± 2.0	0.6448

*(All variables are presented as mean ± SD. * : significant difference (p<0.05) between EPV group and BPV group. †: N=8 for EPV group and N=10 for BPV group. VO_2peak: peak oxygen uptake, % VO_2peak predicted: percentage of predicted value of peak oxygen uptake, HRpeak: heart rate at VO_2peak, O_2/HR: oxygen pulse at VO_2peak, V'Emax: ventilation at VO_2peak, BR: breathing reserve at VO_2peak, Vtmax: tidal volume at VO_2peak, WRmax: work rate at VO_2peak.)*

Table 4: Multiple linear regression with the %VO2peak predicted as the outcome

Predictors	**β**	**SE**	**p-value**
O_2/HR (mlO_2/beat)	3.90306	1.39694	0.0152*
WRmax (W)	0.23985	0.09255	0.0224*
VT1 (ml/min)	-0.00169	0.01711	0.9227
VT2 (ml/min)	-0.00195	0.01295	0.8829

(: significant predictor ($p<0.05$) of $\%VO_2peak$ predicted. O_2/HR: oxygen pulse at VO_2peak, WRmax: work rate at VO_2peak, VT1: first ventilatory threshold, VT2: second ventilatory threshold.)*

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
18/10/18	Bespreking studiedesign + data	Promotor: Copromotor: Student(e): Wegtjens Student(e):
1/2/19	Evaluatie studiedesign	Promotor: Copromotor: Student(e): Wegtjens Student(e):
20/2/19	data verzameling in Rebo	Promotor: Copromotor: Student(e): Student(e): Wegtjens
24/5/19	Bespreking resultaten & discussie	Promotor: Copromotor: Student(e): Student(e): Wegtjens
		Promotor: Copromotor: Student(e): Student(e):
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