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FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
*master in de revalidatiewetenschappen en de
kinesitherapie*

Masterproef

The oxygen uptake efficiency slope during submaximal exercise can be used
to predict peak oxygen uptake in heart failure patients

Promotor :
Mevrouw Ines FREDERIX

Copromotor :
Prof. dr. Dominique HANSEN

Lore Enis , Wouter Roosen

*Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen
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Research context

The European society of Cardiology guideline provides sufficient evidence (based on improvements in physical fitness and cardiovascular risk profile) to include exercise training in a cardiac rehabilitation program (Class IA) for heart failure (HF) patients [1]. Despite this recommendation, it is difficult to promote long-term adherence to exercise prescription in these patients. Despite significant improvements in exercise capacity and cardiovascular risk profile due to exercise training, decrements in these parameters are often observed after completion of supervised exercise training in the long term [2,3]. Therefore, there is a need for novel strategies/devices that can potentially increase long-term participation into exercise training interventions or increased physical activity.

This thesis was part of a larger study which involves Electrically assisted bicycles (EAB) and is still in progress. EAB's could provide us an alternative to motivate patients in achieving their physical activity recommendations. Long-term adherence is hereby enhanced by reducing the difficulties with classical outdoor cycling (strong contrary wind, hilly courses) and/or with physical limitations (low physical fitness, orthopedic limitations). However, before they can be included in physical activity recommendations for HF patients, it should be studied whether this kind of training elicits sufficient exercise intensities and volumes as described in physical activity guidelines.

The research protocol of this study was already determined. Our first task was to recruit HF patients by screening the databases from the Jessa Hospital in Hasselt. Secondly, we contacted those patients to deliver them information of the study and to confirm their inclusion. They were then invited for an initial Cardiopulmonary exercise test (CPET), performed by us and our colleagues, to determine the baseline characteristics and assure medical safety. Thereafter, we analysed the CPETs and tested if the oxygen uptake efficiency slope (OUES) can be used as an alternative parameter for determination of $\text{VO}_{2\text{peak}}$ when submaximal exercise tests are executed in HF patients.

1. Abstract

Objective: In heart failure patients with a reduced ejection fraction (HFREF), executing a cardiopulmonary exercise test (CPET) to assess peak oxygen uptake ($\text{VO}_{2\text{peak}}$) can sometimes be difficult, leading to the inability to execute a maximal exercise test. The aim of this study was to examine whether the oxygen uptake efficiency slope (OUES) can be used as an alternative parameter to estimate $\text{VO}_{2\text{peak}}$ in HFREF patients when submaximal CPET's are executed.

Methods: 37 HFREF patients (30 men, 7 women, mean age 65 ± 8 years) with a mean BMI of $28 \pm 5.4 \text{ kg/m}^2$ and mean left ventricle ejection fraction (LVEF) $30 \pm 7\%$ were included. They performed a maximal CPET on a cycle ergometer (men: $30 \text{ W} + 15 \text{ W/min}$, women: $20 \text{ W} + 10 \text{ W/min}$). The OUES (during exercise tests up to 100%, 75% and 50% $\text{VO}_{2\text{peak}}$), $\text{VO}_{2\text{peak}}$ and first ventilatory threshold (VT1), were determined. Data were analysed in JMP pro v. 12. Relations were examined with Pearson correlations and a linear regression model was built to predict $\text{VO}_{2\text{peak}}$ from age, length, weight, gender and OUES.

Results: The OUES correlated significantly with $\text{VO}_{2\text{peak}}$ and VT1 ($r=0.84$, $p<0.0001$ and $r=0.81$, $p<0.0001$ respectively). Correlations between OUES and $\text{VO}_{2\text{peak}}$ remained significant in HFREF patients within NYHA I ($r=0.97$, $p<0.0001$), NYHA II ($r=0.88$, $p<0.0001$) and NYHA III ($r=0.85$, $p=0.0019$). In submaximal exercise tests, OUES correlated significantly with $\text{VO}_{2\text{peak}}$ (up to 75% $\text{VO}_{2\text{peak}}$: $r=0.80$, $p<0.0001$, and up to 50% $\text{VO}_{2\text{peak}}$: $r=0.82$, $p<0.0001$). $\text{VO}_{2\text{peak}}$ can be predicted by OUES ($r^2=0.80$, $p<0.0001$) by: $1520.468 + (0.77052 \times \text{OUES}) - (14.23932 \times \text{Age}) - (4.629415 \times \text{Weight (kg)})$.

Conclusion: the OUES correlates with $\text{VO}_{2\text{peak}}$ and VT, and can be used to accurately predict $\text{VO}_{2\text{peak}}$ in HFREF patients when a submaximal CPET is executed.

2. Introduction

Heart failure (HF) is one of the most rapidly growing cardiac diseases worldwide, with over one million new diagnoses each year. In Belgium, this translates into 15.643 new cases every year in which men and women are both equally susceptible. It is fatal for more than one quarter of the patients in the first year after diagnosis [15].

HF occurs when the heart is no longer able to deliver sufficient blood to meet the body's needs. The most common signs and symptoms of HF are shortness of breath (dyspnea), fatigue and swelling of the ankles, feet, legs, abdomen and/or neck veins. These symptoms are the consequence of fluid buildup in the body and will, in most cases, occur for the first time after a physical effort such as climbing stairs. As the heart grows weaker, the symptoms will occur at lower exercise intensities and eventually without the provocation of physical exertion to the point of having dyspnea at rest. In order to stabilize the heart's function, increase the functional capacity, and decrease mortality, patients are typically prescribed diuretics, ACE-inhibitors, calcium-antagonist and/or β -blockers. Other medications, such as digoxin, can also be prescribed. Besides medication, there are certain effective devices, such as an Implantable Cardioverter-Defibrillator (ICD) which prevents death due to lethal rhythm disorders such as sustained ventricular tachycardia or fibrillation by delivering an electric shock to the heart and thus re-instigating a sinus heart rhythm. Cardiac Resynchronization Therapy (CRT), which is another implantable device, is a pacemaker that has three leads, one in the right atrium, one in the left ventricle and one in the right ventricle. It synchronizes the ventricular contraction of the heart and therefore increases the pump's efficiency [16].

Cardiopulmonary exercise testing (CPET) with gas exchange analyses is an important examination technique for clinical follow-up of HF patients. It quantifies exercise tolerance and verifies medical safety of exercise training, and is useful for guiding the patient in cardiac rehabilitation. It has also been shown to be of particular value in selecting patients who would benefit from heart transplantation [17,18]. The peak oxygen uptake (VO_{2peak}) reliably reflects cardiopulmonary capacity and serves as a good prognostic marker for HF patients. [11].

However, the VO_{2peak} is sometimes underestimated or not achieved and thus, is less reliable. This may occur when HF patients display insufficient motivation to exercise up to

the point of exhaustion, and/or when co-morbidities limit the patients in their physical capabilities (e.g. orthopedic symptoms, malignant cardiac arrhythmias). It thus follows that clinicians are in need of parameters that can accurately predict VO₂peak, even if a submaximal exercise test has been executed [6].

One possible parameter is the first ventilator threshold (VT1). It occurs at a certain point during the CPET where ventilation starts increasing non-linearly, demonstrating an upward deflection point associated with elevated lactate production. [19]. However, VT is generally not accepted to evaluate the status of HF patients, such as mortality [13].

On the other hand, the oxygen uptake efficiency slope (OUES) has recently been described by Baba et al [12] for the first time. This variable is derived from a slope of the relationship between VO₂ and minute ventilation (VE), and appears not to be influenced by the achieved exercise intensity. It is calculated using the following equation: $VO_2 = a \log_{10} VE + b$, where 'a' is the OUES and 'b' is the intercept. [9] A steeper slope or higher OUES represents a more efficient VO₂, whereas a shallower slope or lower OUES represents a higher VE required for any given VO₂ (see figure 1) [6].

Indeed, two studies have shown that the OUES correlates significantly with VO₂peak in HFREF patients [20,21]. However, it remains to be shown that the OUES may accurately predict VO₂peak when submaximal exercise tests are executed.

Therefore, in this study it was examined whether OUES correlates with VO₂peak and VT1 in HFREF patients, and whether OUES can predict VO₂peak when a submaximal exercise test is executed. We hypothesized that after execution of a submaximal exercise test, VO₂peak can be predicted accurately by use of the OUES slope in HFREF patients.

3. Methods

3.1. Study design

This study (registry number: 16.04/CARDIO16.02) was a mono-center, cross-sectional study run at Jessa Hospital (Hasselt) in Belgium between November 2015 and May 2016.

3.2. Outcomes

3.2.1. Primary outcomes

Primary outcome measures in this study were the oxygen uptake efficiency slope (OUES in $[\text{ml}/\text{min O}_2]/[\log \text{ L}/\text{min VE}]$), peak oxygen uptake ($\text{VO}_{2\text{peak}}$ in ml/min), and the first ventilator threshold (VT_1 in ml/min).

3.2.2. Secondary outcomes

Secondary outcome measures in this study were Gender, Age (years), Length (cm) and Weight (kg).

3.3. Participants

3.3.1. Sample size calculations

An a priori sample size calculation yielded 20 patients necessary to detect an expected univariate correlation of $r=0.7$ between the primary outcome measures (OUES and $\text{VO}_{2\text{peak}}$) [20,21] Statistical power was set on 95% and a 2-sided type I error level of 0.05 was used. GPower v3.1 was used for the sample size calculation.

3.3.2. Patient Population

For patient recruitment, the HF database from the Jessa hospital (Hasselt) was used. Inclusion was based on following criteria:

1. Heart failure as primary indication for cardiac rehabilitation (diagnosis according to the criteria of the European Society of Cardiology) [1].

- a) Symptoms typical of heart failure (HF) e.g. dyspnea on exertion, orthopnea (shortness of breath while lying down) and/or paroxysmal dyspnea (shortness of breath at night).
 - b) Signs typical of HF such as peripheral edema and/or jugular venous distension.
 - c) Reduced left ventricular ejection fraction (LVEF $\leq 35\%$).
2. Age > 50 and < 85 years.
 3. New York Heart Association (NYHA) class: I-IV. See figure 2.
 4. Written informed consent.
 5. Clinically stable for > 4 weeks.
 6. Optimal medical treatment for > 4 weeks.

Patients were excluded in case of significant pulmonary disease (Tiffeneau < 0.70 , FEV1 $< 50\%$ i.e. GOLD III-IV), inability to exercise or musculoskeletal/neurological conditions that may intervene with the cardiopulmonary exercise test (CPET), signs of ischemia or exercise induced cardiac arrhythmias by initial CPET or participation in another clinical trial.

3.4. Maximal cardiopulmonary exercise test (CPET)

The patients performed a maximal CPET [4,5] with breath-by-breath gas exchange analysis on an electrically braked cycle ergometer (Jaeger MS-CPX) between 9 a.m. and 4 p.m. We used a ramping protocol consisting of a 30Watt (W) start, 15W increase every 60 seconds for males and a 20W start, 10W increase every 60 seconds for females.

The test was considered maximal in case of an achieved heart rate $>85\%$ of the maximal predicted heart rate and/or a respiratory gas exchange ratio (RER) >1.1 and/or a ventilatory reserve (VR: Peak Ventilation (VE Peak) • Maximal Voluntary Volume (MVV)-1) $>80\%$. All subjects achieved these criteria.

Patients were instructed to cycle at 70 revolutions per minute (rpm), and the test was terminated when the patient was no longer able to cycle >59 rpm. Oxygen consumption (VO₂), minute ventilation (VE), carbon dioxide output (VCO₂) and heart rate (HR), measured by an electrocardiogram, were measured and averaged every 10 seconds throughout the test. Patients performed the CPET during similar times of the days and one hour after a

standard meal (providing 367 kcal, consisting of 27% of energy from carbohydrates, 19% from protein, and 54% from fat).

3.4.1. Calculations.

Length was determined in centimeters using a measuring staff fixed to the wall. Patients were asked to stand straight against the wall on bare feet, with their heels touching the wall.

Weight was measured in kilograms using an analog scale. Patients were weighed without shoes.

Peak VO_2 during maximal CPET was defined by the mean of the three highest consecutive 10-second measurements (at least 8 seconds of 10) before the CPET was terminated.

The oxygen uptake efficiency slope (OUES) was computed by a linear least squares regression from the oxygen uptake on the logarithm of the minute ventilation according to the following equation: $\text{VO}_2 = a \log_{10} \text{VE} + b$, where 'a' is the OUES and 'b' is the intercept.

OUES was also calculated within maximal exercise tests artificially aborted at 75% and 50% of $\text{VO}_{2\text{peak}}$. For the determination of OUES at 75% and 50% $\text{VO}_{2\text{peak}}$, a perpendicular line was drawn at 75% and 50% $\text{VO}_{2\text{peak}}$ on the y-axis of the graph. We then projected a line from this point onto the x-axis. Finally, the OUES was calculated between the start point of the graph and the projection on the x-axis (See figure 3).

VT1 was determined using all three of the following criteria (see figure 4):

- First inflection point in the VE over time graph (1st Wasserman)
- Increase of the VE/ VO_2 slope without a simultaneous increase of the VE/ VCO_2 slope in the VE/ VO_2 over time graph (6th Wasserman)
- Increase of the End Tidal Pressure of Oxygen (PETO_2) in the PETO_2 over time graph (9th Wasserman)

3.4.2. Ethics

This study was approved by the local medical ethical committee (Jessa Hospital and Hasselt University, Hasselt, Belgium), and the study conformed to the standards set by the latest revision (2013) of the Declaration of Helsinki. After careful explanation about the nature and risks of the experimental procedures, all subjects gave their written informed consent before participating in the study.

3.5. Statistical analysis

Statistical analyses were executed by using JMP pro v. 12. All assumptions for normal data distribution were checked and confirmed. First, statistical independency was assured. Second, the normality of the residuals of the dependent variable (VO₂peak) was checked by a normal quantile plot and a goodness of fit analysis (Shapiro-Wilk W test $p < 0.05$). Third, the homoscedasticity was checked by comparing the predicted values (x-axis) and the residuals (y-axis) of the dependent variable. To achieve this, the points had to be equally distributed in a strip without the forming of any pattern. Finally, the linearity was checked by comparing the residuals of the dependent variable (VO₂peak) on the y-axis with the independent variable (OUES, VT₁) on the x-axis. The points had to be randomly distributed so no patterns could be seen. There was no need for any correction. Data were expressed as mean \pm standard deviation (SD). Relations between parameters were examined by Pearson correlations (relation between two ratio variables). A linear regression model was built to predict VO₂peak (dependent variable) from age, length, weight, gender and OUES (independent variables), and this within exercise tests executed up to 100%. Statistical significance was set at $p < 0.05$ (2-tailed).

4. Results

4.1. Participant characteristics

Our total study population consisted of 37 HFREF patients, after having screened a database of 2500 patients, and contacted 650 patients (See figure 5).

The demographics and exercise characteristics are presented in Table I. Our sample included thirty men and seven women. Patients were on average $65 \pm 8,4$ years old with a BMI of $28 \pm 5 \text{ kg/m}^2$. LVEF was $30 \pm 7 \%$. Nine patients were in NYHA class I, eighteen in NYHA class II and ten in NYHA class III. Only nine patients had a form of non-ischemic cardiomyopathy (CMP), the other 28 patients suffered from ischemic CMP. Six patients had type 2 diabetes mellitus as a co-morbidity, twenty-three patients suffered from hypertension, twenty-seven patients suffered from hyperlipidaemia, twenty-four patients were susceptible to a hereditary factor regarding heart disease (first degree relative(s) who also suffered from a cardiac problem) and three patients still actively smoked. Seventeen patients had an Implantable Cardioverter Defibrillator (ICD). One patient had a Cardiac Resynchronisation Therapy device which also contained a Defibrillator (CRT-D device). Twenty-seven patients (73%) took ACE-inhibitors, twenty-four (65%) took diuretics, thirty (81%) took statins and nine (24%) took anti-arrhythmics. Twenty-six (72%) of the patients took β -Blockers.

The outcomes of the cardiopulmonary exercise test are as follows: The average $\text{VO}_{2\text{peak}}$ was $1302 \pm 454,0 \text{ ml/min}$, which corresponded with $73 \pm 19.4\%$ of the predicted maximum. Further, the average W_{peak} was $120 \pm 41,2 \text{ W}$, which corresponded $98 \pm 29.1\%$ of the predicted maximum. The average maximal heart rate (MaxHR) was $116 \pm 19,2 \text{ beats per minute (bpm)}$, which corresponded with $76 \pm 10,3\%$ of the predicted maximum. All subjects reached a peak respiratory gas exchange ratio (RER_{peak}) of exactly 1.22 ± 0.1 . The foremost reasons for terminating the exercise test were leg fatigue in thirty patients (81%) and dyspnoea in five patients (14%), though in most patients, a combination of both leg fatigue and dyspnoea was responsible for terminating the test.

4.2. correlations between OUES, VO2peak and VT1.

OUES correlated significantly with VO2peak ($r = 0.85$, $p < 0.0001$) (see figure 6). In addition, OUES correlated significantly with VT1 ($r = 0.83$, $p < 0.0001$) (see figure 7), and VO2peak correlated significantly with VT1 ($r = 0.76$, $p < 0.0001$) (see figure 8).

4.3. correlations between OUES and VO2peak within different NYHA classes.

In the NYHA I group, OUES correlated with VO2peak ($r = 0.97$, $p < 0.0001$). In NYHA II, the correlation was slightly less with $r = 0.88$ ($p < 0.0001$). This downwards trend continued as the correlation in NYHA III was $r = 0.85$ ($p = 0.0019$) (See figure 9).

4.4. correlations between OUES at 75% and 50%VO2peak and VO2peak.

For the entire sample, OUES at 75%VO2peak correlated significantly with VO2peak ($r = 0.80$, $p < 0.0001$) (see figure 10). IN addition, OUES at 50% VO2peak correlated significantly with VO2peak ($r = 0.82$, $p < 0.0001$). (see figure 11). In NYHA I the correlation at 75%VO2peak was $r = 0.84$ ($p = 0.0043$) and at 50%VO2peak it was $r = 0.84$ ($p < 0.0051$) (see figure 10). In NYHA II patients the correlation at 75%VO2peak was $r = 0.83$ ($p < 0.0001$) and at 50%VO2peak it was $r = 0.85$ ($p < 0.0001$). (See figure 12). At last, in NYHA III patients, the correlation at 75%VO2peak was $r = 0.73$ ($p < 0.0165$) and at 50%VO2peak it was $r = 0.69$ ($p < 0.394$). (See figure 13).

4.5. Regression analysis to predict VO2peak.

The following regression formula was created to predict VO2peak ($r^2 = 0.80$, $p < 0.0001$):

$$\text{VO2peak} = 1520.468 + (0.77052 \times \text{OUES}) - (14.23932 \times \text{Age}) - (4.629415 \times \text{Weight (kg)}).$$

5. Discussion

In this study, it was found that the OUES correlates significantly with VO₂peak and VT1 in HFREF patients. This study is the first to offer a regression formula that can be used by clinicians to predict VO₂peak by use of OUES in HFREF patients, even in case of submaximal exercise tests.

VO₂max is still proclaimed as the golden standard in evaluating the cardiorespiratory functional reserve because it is an index of the response of all of the mechanisms involved with exercise [7]. However, to actually reach the necessary 'plateau' to acquire the VO₂max turns out to be a difficult task for many, especially elderly heart failure patients. Therefore, the VO₂peak is widely used as a substitute for the VO₂max as a prognostic tool for evaluating patients with heart failure [8].

Our results confirm previous studies that OUES correlates significantly with VO₂peak ($r=0.85$, $p<0.0001$) in HFREF patients [20,21]. In addition, OUES even correlated significantly with VT1 in HFREF patients. The latter finding is, as far as the authors are aware, not yet discovered. It thus follows that OUES is closely related to different indicators of exercise tolerance in HFREF patients. The OUES is especially praised as a valuable submaximal parameter by the study of Baba et al. [9] because of its robustness to exercise intensity, meaning that the use of submaximal exercise data does not greatly alter the results, and therefore, does not reduce its usefulness as an index of the functional impairment of heart failure. Indeed, OUES at 100% of VO₂peak does not differ significantly from OUES at 75% and 50% of VO₂peak, as indicated previously of Hollenberg et al. [14]. Furthermore, and in line with the findings from Hollenberg et al [14], OUES at 50% ($r=0.82$, $p<0.0001$) or 75% ($r=0.80$, $p<0.0001$) of VO₂peak correlates significantly with VO₂peak, indicating that OUES is independent of exercise effort.

We examined HFREF patients. There is not yet any evidence that OUES and VO₂peak correlate well in HF patients with preserved ejection fraction (HFPEF), yet several studies have shown that they do correlate well in patients with coronary artery disease (CAD) [25,26,27]. This means that in other cardiac populations, OUES can prove to be useful as well

in predicting VO₂peak. The correlation in the different NYHA groups are all significant. However, we saw a small decline in correlation coefficients from NYHA I to NYHA III. This could mean that the OUES is less accurate in predicting the VO₂peak in weaker HF patients.

There are several reasons as to why we may prefer OUES to determine exercise tolerance in HFREF patients. First of all, and shown by our data, HFREF do not need to achieve a maximal exercise test to accurately predict VO₂peak. For this reason, a regression formula is now provided for this purpose: $VO_2\text{peak} = 1520.468 + (0.77052 \times \text{OUES}) - (14.23932 \times \text{Age}) - (4.629415 \times \text{Weight (kg)})$. The OUES has been demonstrated to follow VO₂peak changes induced by exercise training and increases by implementing both moderate continuous training [25,28,29,30] and high intensity training [31], in patients with HF and CAD. It may thus be anticipated that also during follow-up of HFREF patients, such regression formula can be used. However, the latter assumptions remain to be confirmed experimentally. Moreover, the OUES measurement is free from intra-observer and inter-observer variability, because it is determined mathematically from gas exchange data. It is however, still possible to acquire a different OUES between researchers, depending on how the calculation was made. For example, if one researcher uses the entire data of the test to calculate the OUES, thus putting the calculating thresholds at the beginning and the end of the test, he or she might find a different value for the OUES than the other researcher whom only uses a part of the data (and thus, not utilizing the entirety of the VE and VO₂ data on the graph that is presented). Furthermore, the OUES provides us with information about the different systems in the body and their interaction during exercise, based on the development of metabolic acidosis, which is controlled by the distribution of blood to the skeletal muscles. It is also modified by the physiological dead space, which is affected by the perfusion to the lungs. And thus, limiting factors of the OUES are: carbon dioxide (CO₂) production from the muscle's aerobic metabolism, pH buffering by bicarbonates, the arterial pressure of carbon dioxide (PCO₂) and the physiological dead space [9]. Therefore, a good OUES shows a great amount of working muscle mass, a fast and unimpaired blood flow to the muscle, efficient O₂-extraction and utilization by the muscles, a delayed appearance of lactate acidosis and a good structural integrity and perfusion of the lungs. There is also a relationship seen with age, whereas in an older subject, a declined OUES is expected [14,23]. Being overweight or obese might also have an impairing effect on the OUES, because of obesity's effects on all

the previously discussed limiting factors [22]. The study by Drinkard et al. [22] also addressed a possible under-prediction of the VO₂peak at higher fitness levels and over-prediction of the VO₂peak at lower fitness levels, using the OUES in overweight participants. This, because of a bias found in the overweight group. As thirty of our patients were overweight (Average BMI: 28), we should be wary of these findings.

In this study, good correlations were found between the first ventilatory threshold (VT1) and OUES ($r = 0.83$, $p < 0.0001$) or VO₂peak ($r = 0.76$, $p < 0.0001$) were found. The VT1 is another parameter that can be used as a submaximal estimate for aerobic power, which also increases by exercise training. It increases significantly with moderate continues training [25,30,31,32], but even more so with high intensity training [32,33], in both patients with HF as well as coronary artery disease.

This study was prone to some limitations. Despite reaching the calculated number of patients, our sample size was somewhat small and consisted mostly of men. Even though we used generally accepted indicators to check if our CPET tests were indeed maximal (RERpeak > 1.09), some patients were not able to perform to the full extent of their physical abilities, due to the presence of an ICD.

6. Conclusion

In this study, it was found that the OUES correlates significantly with VO₂peak and VT1 in HFREF patients. This study offers a regression formula that can be used by clinicians to predict VO₂peak by use of OUES in HFREF patients, even in case of submaximal exercise tests.

7. References

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8. Appendix

Table I. Clinical, demographic and exercise characteristics. Data are presented as mean with SDs.

Parameter	All (n=37)
Sex (Male, Female)	30,7
Age (yrs)	65 ± 8,4
Body mass index (kg/m ²)	28 ± 5,4
LVEF (%)	30 ± 7,3
ICD (%)	46
β-Blockers (%)	72
ACE-inhib. (%)	73
Diuretics (%)	65
Statins (%)	81
Anti-AR (%)	24
RERpeak	1.22 ± 0.1
Vo2peak (ml/min)	1302 ± 454,0
Vo2peak (% Pred.)	73 ± 19.4
Watt peak (Load)	120 ± 41,2
Watt peak (% Pred.)	98 ± 29.1
HRmax (% Pred.)	76 ± 10,3
VT1 (ml/min)	924 ± 339.1
OUES ([ml/min O ₂]/[log L/min VE])	1441 ± 488,0

Yrs: Years; LVEF: Left ventricular ejection fraction; ICD: implantable cardioverter defibrillator; ACE-inhib.: angiotensin-converting-enzyme inhibitor; Anti-AR: Anti-arrhythmics; RER: respiratory exchange ratio; VO₂: oxygen uptake; HRmax: maximal heart rate; VT1: First ventilatory threshold; OUES: oxygen uptake efficiency slope.

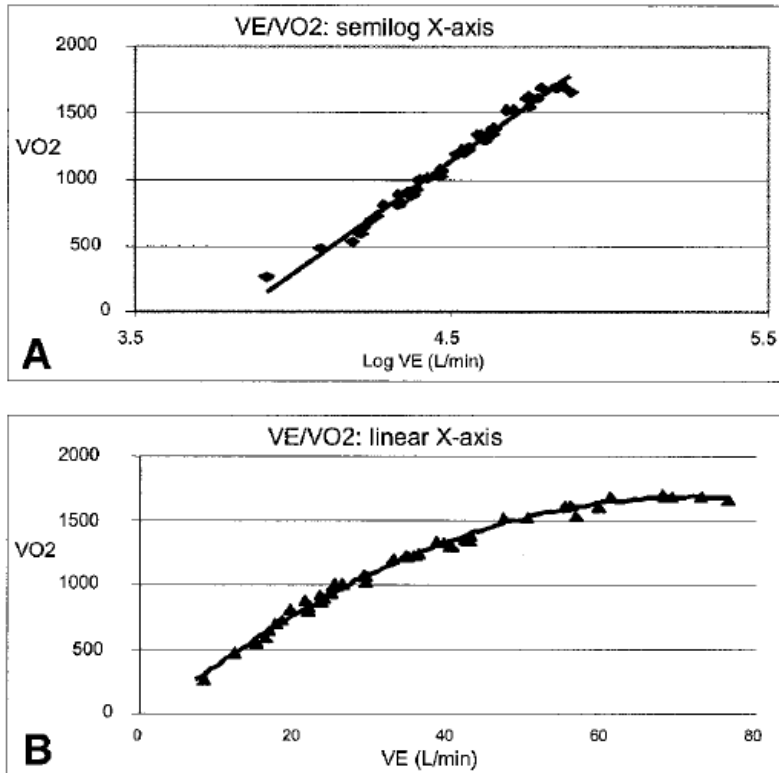


Figure 1. Relationship between VO_2 and VE during an incremental exercise. A. OUES, B. VO_2/VE

Table 2 New York Heart Association functional classification based on severity of symptoms and physical activity

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Figure 2. NYHA classification from ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012.

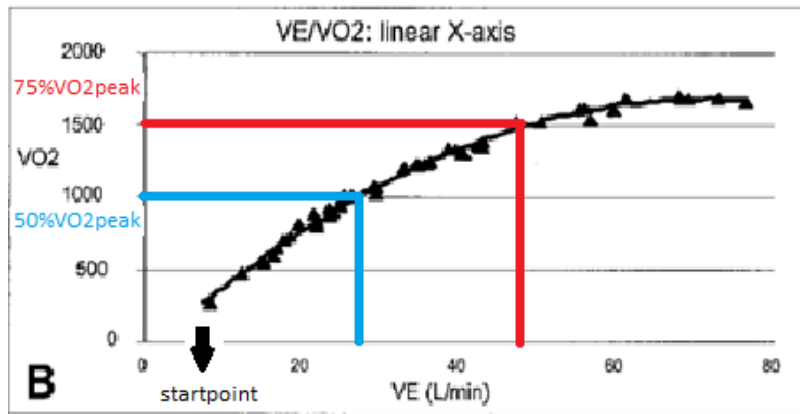


Figure 3. Determination of the 50% and 75% OUES.

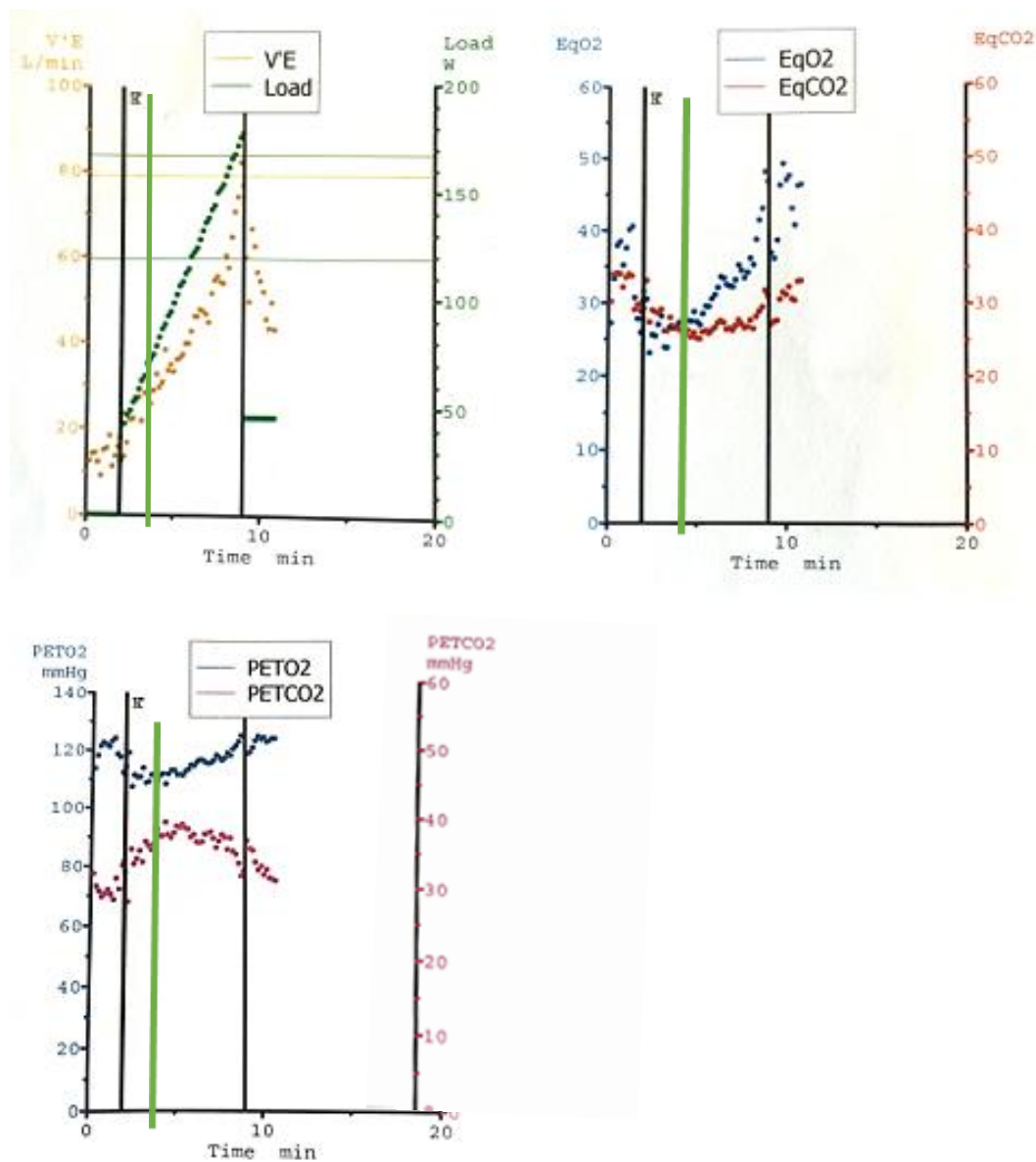


Figure 4. Top left: 1st Wasserman. Top right: 6th Wasserman. Bottom left: 9th Wasserman. The First Ventilatory Threshold (VT1) is indicated by the green line in each plot.

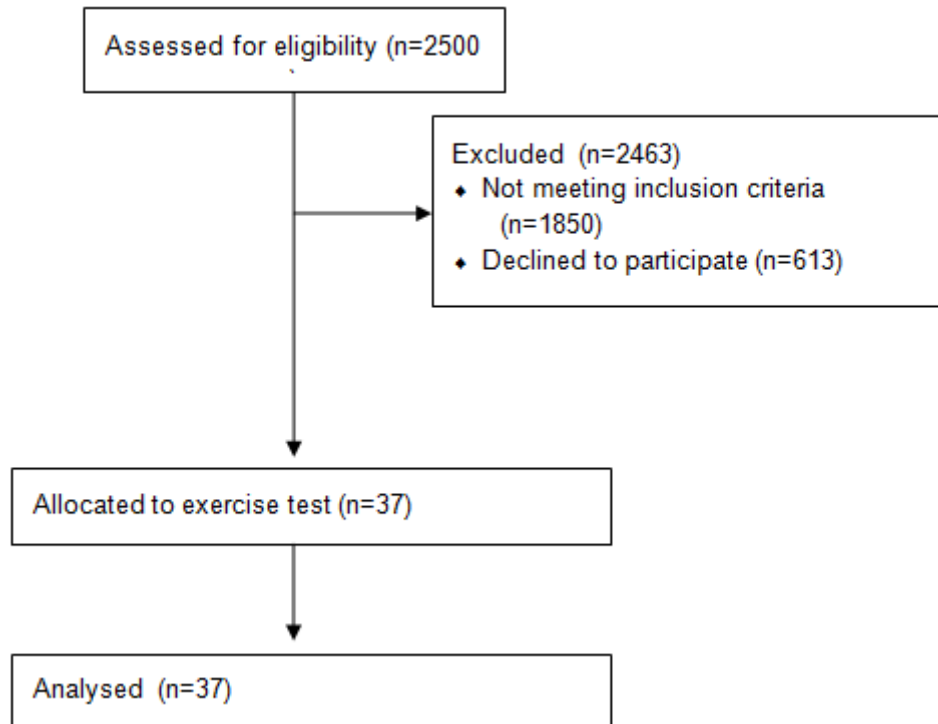


Figure 5. Modified Consort 2010 flow diagram for patient recruitment.

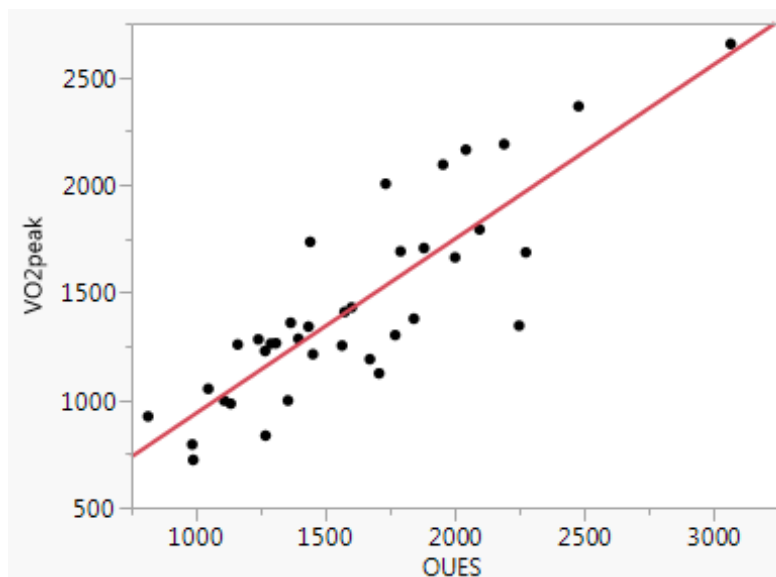


Figure 6. Relationship between the 100%VO₂peak (ml/min) and the 100%OUES ([ml/min O₂]/[log L/min VE]) in all participants ($r=0.85$, $P<0.0001$).

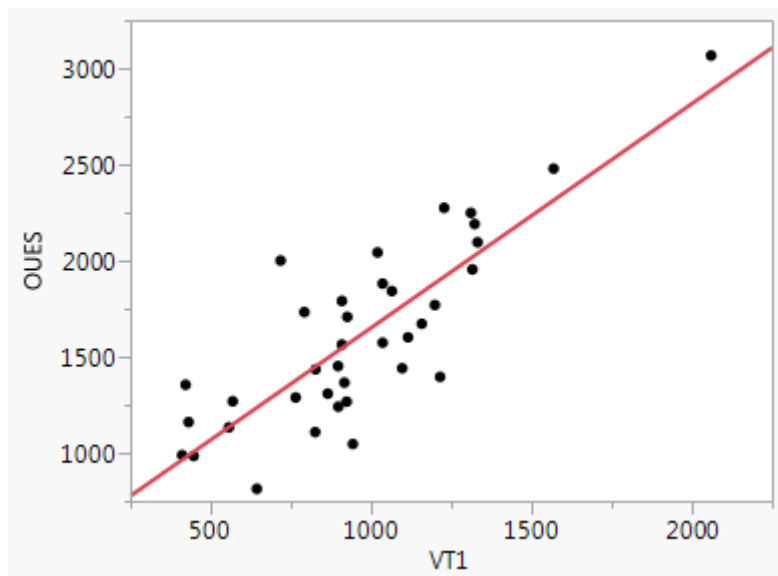


Figure 7. Relationship between the 100%OUES ([ml/min O₂])/[log L/min VE] and the VT1 (ml/min.) in all participants ($r=0.83$, $p<0.0001$).

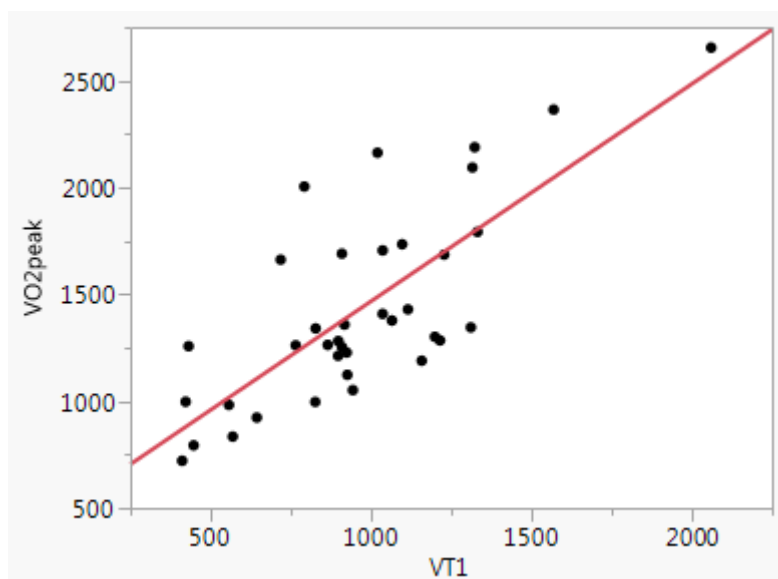


Figure 8. Relationship between the VO₂peak (ml/min.) and the VT1 (ml/min.) in all participants ($r=0.76$, $p<0.0001$).

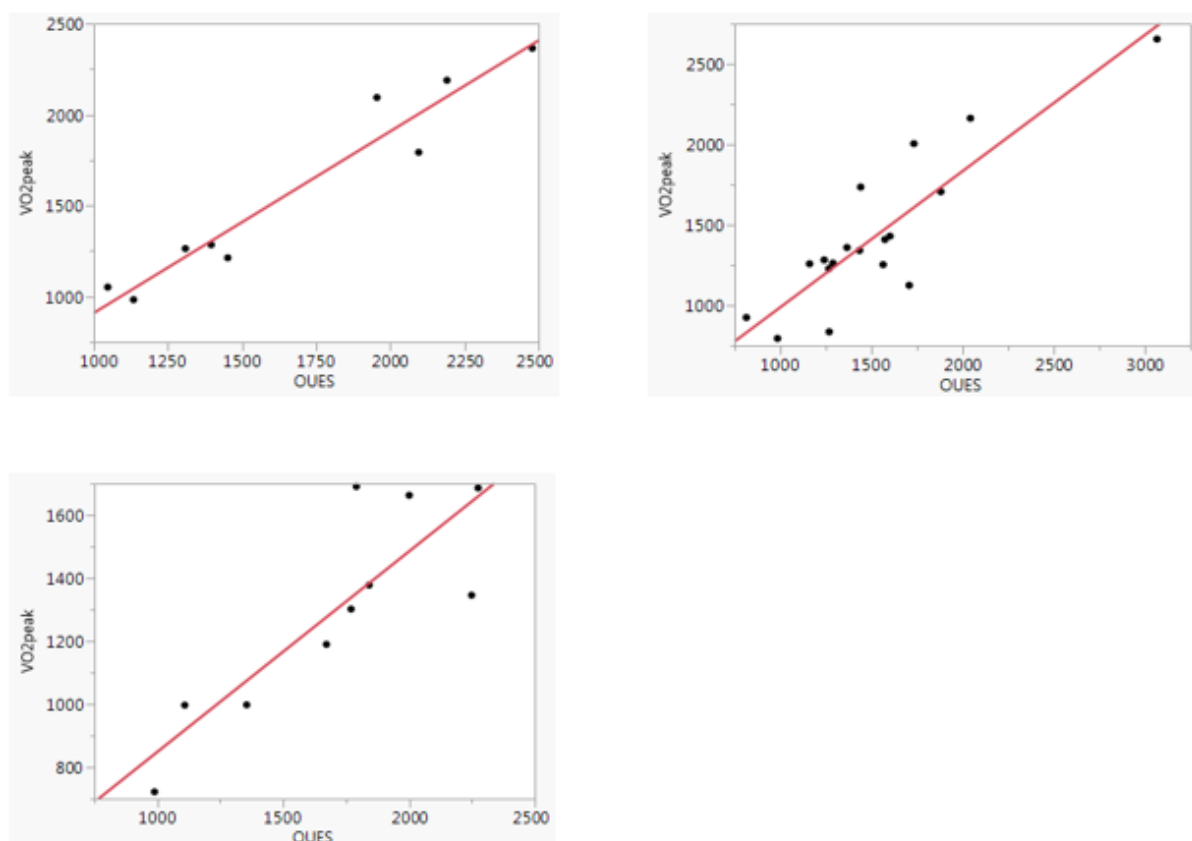


Figure 9. The top left graph shows the correlation between the VO_{2peak} (ml/min.) and the OUES ([ml/min O_2]/[log L/min VE]) in the NYHA I group ($r=0.97$, $p<0.0001$), top right graph in the NYHA II group ($r=0.88$, $p<0.0001$) and the down left graph in the NYHA III group ($r=0.85$, $p=0.0019$).

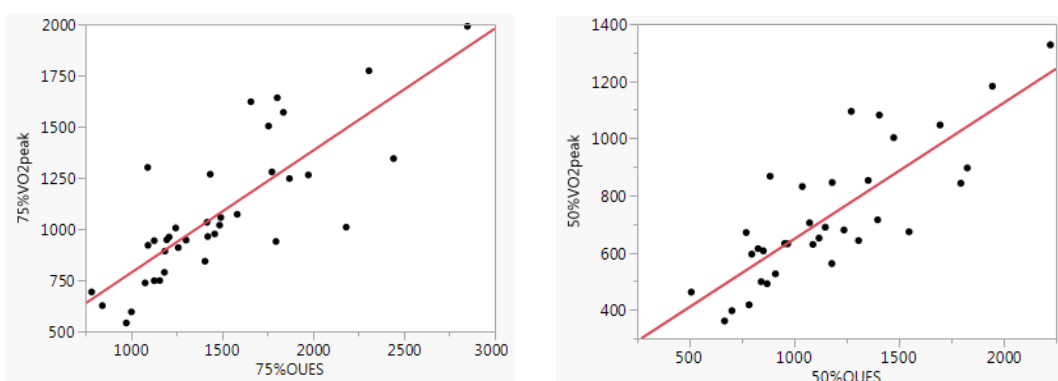


Figure 10. The left graph shows the correlation between the $75\%VO_{2peak}$ and the $75\%OUES$. ($r=0.80$, $p<0.0001$). The right graph shows the correlation between the $50\%VO_{2peak}$ and the $50\%OUES$ ($r=0.82$, $p<0.0001$).

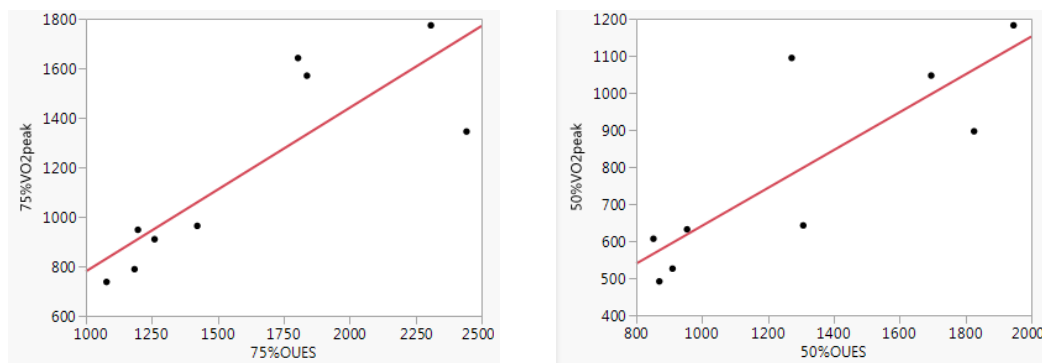


Figure 11. NYHA I group. The left graph shows the correlation between the 75%VO₂peak and the 75%OUES ($r=0.84$, $p=0.0043$). The right graph shows the correlation between the 50%VO₂peak and the 50%OUES ($r=0.84$, $p=0.0051$).

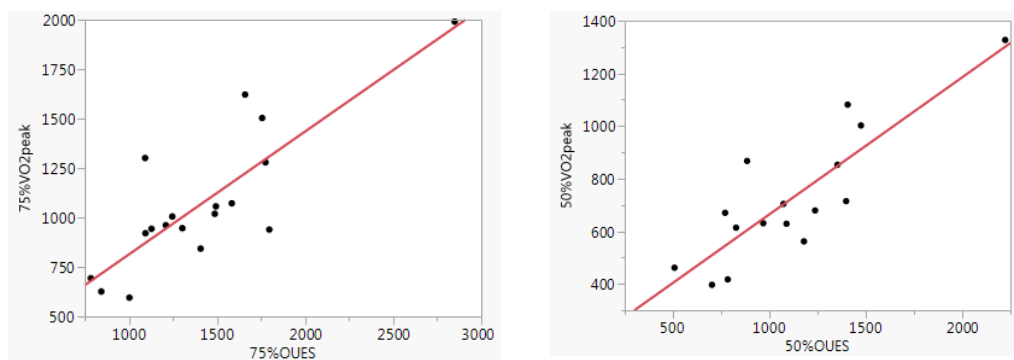


Figure 12. NYHA II group. The left graph shows the correlation between the 75%VO₂peak and the 75%OUES ($r=0.83$, $p<0.0001$). The right graph shows the correlation between the 50%VO₂peak and the 50%OUES ($r=0.85$, $p<0.0001$).

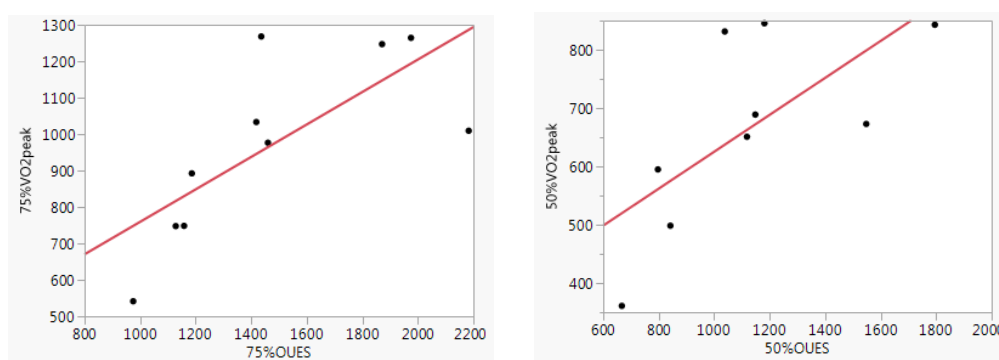


Figure 13. NYHA III group. The left graph shows the correlation between the 75%VO₂peak and the 75%OUES ($r=0.73$, $p=0.0165$). The right graph shows the correlation between the 50%VO₂peak and the 50%OUES ($r=0.69$, $p=0.0394$).

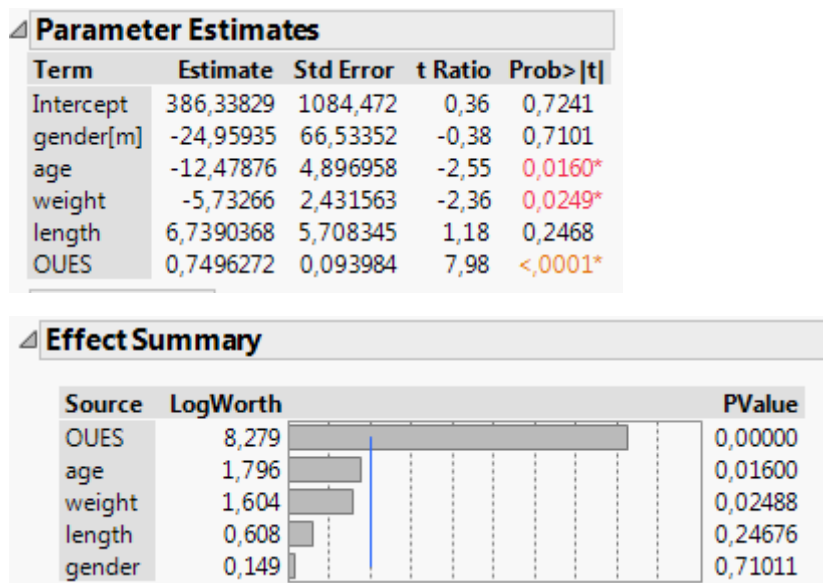


Figure 14. Regression model VO2peak with OUES, age, weight, length and gender.

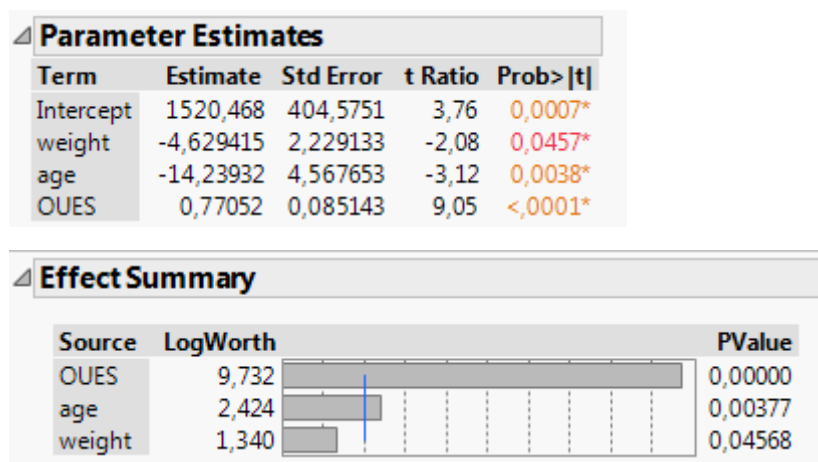


Figure 15. Simplified regression model VO2peak with the OUES, age and weight.

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The oxygen uptake efficiency slope during submaximal exercise can be used to predict peak oxygen uptake in heart failure patients

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij inwendige aandoeningen**

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