Masterproef
The correlation between the oxygen uptake efficiency slope and other cardio pulmonary parameters in heart failure patients

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Wouter Roosen, Lore Enis
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie
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Acknowledgement

The realization of this master’s thesis wouldn’t have been possible without the help of many others. Therefore, we would like to thank our promotor Drs. Frederix Ines and also our co-promotor, Prof. Dr. Hansen Dominique for their support throughout the whole year. They were always ready to assist us and to give us meaningful feedback.

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W.R.
L.E.
Research context

Exercise training, as part of a cardiac rehabilitation program is recommended by the European Society of Cardiology, (Class IA), for heart failure (HF) patients [1]. Despite the proven effectiveness of exercise training in cardiac rehabilitation (improvements in physical fitness and cardiovascular risk profile), long-term adherence to exercise prescription is often disappointing. This translates into suboptimal control of physical fitness and cardiovascular risk profile in the long term [2,3]. Therefore, novel strategies/devices that have the potential to increase long-term participation rates are urgently needed.

Electrically assisted bicycles (EAB) provide patients with an alternative to achieve physical activity recommendations, while at the same time 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 recommended as part of standard cardiac rehabilitation programs for HF patients, it should be studied whether cycling with electrical assistance elicits sufficient exercise intensities and volumes to contribute to meeting the exercise training guidelines.

We were asked to fulfill this study in co-operation with two students from 1st master Rehabilitation science and Physiotherapy. The research protocol was already determined. We started off with the recruitment of HF patients. We searched databases from the Jessa Hospital in Hasselt for patients that met the inclusion criteria. Thereafter we contacted the patients to include them in the study. The patients were invited for an initial Cardiopulmonary exercise test (CPET) performed by the students, to determine the baseline characteristics and assure medical safety.

Our part was to execute the CPETS, analyze them and search for a correlation between the oxygen uptake efficiency slope (OUES), the VO2peak and the first ventilatory threshold (VT1), of which the results will be discussed in this thesis. The whole process was closely supervised and supported by our promotor and co-promotor.
1. **Abstract**

**Objective:** To assess the correlation between the oxygen uptake efficiency slope (OUES), peak oxygen uptake (VO2peak) and the first ventilatory threshold (VT1) in heart failure (HF) patients.

**Methods:** 37 patients with heart failure and a reduced ejection fraction (HFREF) (NYHA II-III, age 65 ± 8.4y, LVEF 30 ± 7.3%) were asked to perform a cardiopulmonary exercise test (CPET). A ramping protocol (30/15/1 for males, 20/10/1 for females) and breath-by-breath gas exchange analysis on an electrically braked cycle ergometer (Jaeger MS-CPX) were used. The OUES was determined according to the following equation: \( VO2 = a \log_{10} VE + b \), where ‘a’ is the OUES, VO2peak was defined by the mean of the three highest consecutive 10-second measurements before exercise terminates and VT1 was determined on the waterman graphs. Correlation between the parameters was examined with a linear regression model on JMP pro 12.

**Results:** A significant correlation was found between the OUES and VO2peak \((r=0.84, p<0.0001)\), the OUES and the VT1 \((r=0.81, p<0.0001)\) as well as between the VO2peak and the VT1 \((r=0.76, p<0.0001)\).

**Conclusion:** We can confirm that the OUES correlates well with the VO2peak and also with the VT1. The correlation between the VO2peak and the VT1 is also significant. Thus, these submaximal parameters can be used in the evaluation of heart failure patients when the patient has failed to achieve a maximal cardiopulmonary exercise test.
2. Introduction

In the evaluation of HF patients, the VO2max is seen as the golden standard [11]. This index is defined as the point where the oxygen uptake reaches a plateau despite increase in work rate. Because this is rarely seen in a CPET, VO2peak is widely used as a substitute. This value is measured at the end of the test. The parameter is also considered to provide great diagnostic and prognostic value. However, VO2peak might be underestimated and thus less reliable when patient motivation is low or different protocols are used. [6] Therefore submaximal parameters like the VT1 and the OUES were introduced to evaluate the cardiopulmonary function.

Despite the use of the VT1 when a CPET isn’t performed maximally, the variable isn’t generally accepted to assess HF patients [13].

The OUES, a more recently reported parameter by Baba et al [12] shows lot of potential in providing more reliable information after a submaximal CPET. This variable derives from a slope of the relationship between oxygen uptake (VO2) and minute ventilation (VE) and appears not to be influenced by the achieved exercise intensity. It’s calculated using the following equation: VO2=a log10 VE+b, where ‘a’ is the OUES and ‘b’ is the intercept. [9] A steeper slope or higher OUES represents a more efficient oxygen uptake, whereas a shallower slope or lower OUES represents a higher amount of ventilation required for any given oxygen uptake (Figure 1) [6].

In our last year review we reported a good correlation between the OUES and VO2peak which proves the potential diagnostic and prognostic value of the OUES. To confirm our findings, we’ll now analyze the relationship between the different parameters after the initial CPET of a new study with HF patients was performed.

We hypothesize a good correlation between the OUES and the VO2peak as well as the VT1 in HF patients.
3. Methods

3.1. Study design

This study (registered at the Clinical Trials registry) is a mono-center, cross-sectional clinical trial run at Jessa Hospital (Hasselt) in Belgium between November 2015 and May 2016.

3.2. Outcomes

3.2.1. Primary outcomes

The correlation between the OUES ([ml/min O2]/[log L/min VE]), the VO2peak (ml/min) and the VT1 (ml/min).

The correlation between the VO2peak(ml/min) and the VT1(ml/min) will also be researched.

3.3. Participants

3.3.1. Sample size calculations

A priori sample size calculation yielded 20 patients necessary to detect an expected correlation of r=0.7 between the primary outcomes. 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 a 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).
   a) Symptoms typical of HF e.g. dyspnea on exertion, orthopnea, paroxysmal dyspnea (NYHA II or III).
   b) Signs typical of HF e.g. peripheral edema, jugular venous distension.
   c) Reduced EF (EF ≤ 35%).
2. Age > 50 and < 85 years.
3. Written informed consent.
5. 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 CPET, signs of ischemia or exercise induced cardiac arrhythmias by initial (CPET) or participation in another clinical trial.

Total study population consisted of 37 HF patients.

3.4. Initial maximal cardiopulmonary exercise test (CPET)

The patients performed an initial maximal CPET [4,5] with a ramping protocol (30/15/1 for males, 20/10/1 for females) and breath-by-breath gas exchange analysis on an electrically braked cycle ergometer (Jaeger MS-CPX).

The test is considered maximal in case of an achieved heart rate >85% of the maximal predicted heart rate, a respiratory gas exchange ratio (RER) >1.1, and/or a ventilatory reserve (VR: VE peak•MVV-1) >80%.

Patients are instructed to cycle at 70 rpm, and the test is ended when the patient is no longer able to cycle >59 rpm. Oxygen consumption (VO2), minute ventilation (VE), carbon dioxide output (VCO2) and heart rate (HR) are measured and averaged every 10 seconds throughout the test. Patients will perform CPET during similar times of the days and one hour after a standard meal (366,52 kcal).

Peak VO2 during maximal CPET is defined by the mean of the three highest consecutive 10-second measurements (at least 8 seconds of 10) before exercise terminates. Max HR is defined as the absolute highest HR reached in the last phase of active exercise testing.

VE/VCO2 slope was calculated by linear regression analyses of the relation between VE and VO2 during the entire CPET.

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: \( VO2 = a \log_{10} VE + b \), where ‘a’ is the OUES and ‘b’ is the intercept.
3.5. Biometrical aspects

3.5.1. Primary end points: The OUES, The VO2peak and the VT1.

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.

Peak VO2 during maximal CPET is defined by the mean of the three highest consecutive 10-second measurements (at least 8 seconds of 10) before exercise terminates.

VT1 will be determined by a trained student using following criteria:

- First infliction point in the VE over time graph (1st Wasserman)
- Increase of the VE/VO2 slope without a simultaneous increase of the VE/VCO2 slope in the VE/VO2 over time graph (6th Wasserman)
- Increase of the PETO2 in the PETO2 over time graph (9th Wasserman)

3.6. Individual study procedure

3.6.1. Patient information and informed consent

The investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail to each participant.

Each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship to the treating physician. The patient should be provided with enough time to think about the participation in the study. The Informed Consent should be given by means of a standard written statement. The participant should read the statement and consider his/her decision before signing and dating the document, and should be given a copy of the signed document.
3.6.2. Withdrawal of informed consent

Patients may withdraw their consent to participate at any time of the study without giving the reason for it. Nevertheless, the patient should be asked for the reason of the premature termination after being informed that he/she does not need to answer this question. Date of enrolment and date of and reason for withdrawal are to be documented in any case. The patient is to be informed that in case of revocation of his/her consent, the stored data may be used further.

3.7. Statistical analysis

Everything was calculated using JMP pro 12. The results from the baseline characteristics are expressed as the mean value with the standard deviation (SD), calculated by distribution. The relationship between the OUES and the VO2peak, between the OUES and the VT1 and between the VO2peak and the VT1 were assessed by linear regression analysis. All assumptions, including the linearity, statistical independence, homoscedasticity and the normality were checked and corrected if it was needed. A level of p<0.05 was considered to be statistically significant.
4. Results


Demographics and exercise characteristics are presented in Table I. 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 Diabetes Mellitus type II 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 and three patients still actively smoked.

Seventeen patients had an ICD. One patient had a CRT-D. Four patients still reported episodes of dizziness due to their heart failure while ten patients suffered from dyspnoea during exercise.

All of the included patients reached a maximal exercise test (RERpeak ≥1.1 minimum) even when the test had to be terminated prematurely. The reasons for terminating the exercise test are given as follows: Leg fatigue in thirty patients (81%), dyspnoea or a sense of breathlessness in five patients (14%), and the reaching of the ICD threshold’s heartbeat in two patients (5%).

4.2. The correlation between the OUES, the VO2peak and the VT1.

The values for the OUES and the VO2peak correlated significantly (r = 0.84, p<0.0001), see figure 2.

The values for the OUES and the VT1 also correlated significantly, though slightly less so than with the VO2peak (r = 0.81, p<0.0001), see figure 3.

The correlation between the VO2peak and VT1 was also significant, though less than the previous correlations (r = 0.76, p<0.0001), see figure 4.
5. Discussion

This study found that the OUES, at maximal exercise intensity has a significant correlation with the VO2peak as well as with the VT1. The VO2max is still the 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 very difficult for many, especially older, heart failure patients. Therefore, the VO2peak is widely used as a substitute prognostic tool for evaluating patients with heart failure [8]. As our results depict, the excellent correlation between the OUES and the VO2peak in patients with heart failure is proof that we should be able to use the OUES in predicting the VO2peak and thus using it as a tool for evaluation. The OUES has certain advantages in contrary to the VO2peak since the patient doesn’t need to achieve a maximal effort in the exercise test to gain the correct measurement of the OUES [9]. It can be determined in all patients. Moreover, this measurement is free from intra-observer and inter-observer variability, because it is determined mathematically from gas analysis data. Further, the OUES can tell us a lot about different systems in the body and their interaction during exercise. CO2 production from the muscle aerobic metabolism and the PH buffering by bicarbonate, arterial PCO2 and physiologic pulmonary dead space ventilation are all factors that influence the OUES. So, a good OUES shows a great amount of working muscle mass, a fast and unimpaired blood flow to the muscle, an efficient O2-extraction and utilization by the muscles, a delayed appearance of lactate acidosis and a good structural integrity and perfusion of the lungs [14]. There’s also a relationship seen with age, whereas in an older subject a declined OUES is expected [14].

The VT1 is another parameter that can be used as a submaximal estimate for aerobic power. It is, however, prone to inter-observer and intra-observer variability [10] and cannot always be calculated in every patient, though we did not have this problem with our study. It is because of the sturdiness of the OUES to the level of exercise intensity, as well as its correlation to the VO2peak and the VT1 that we believe it is an important tool to use in the evaluation of heart failure patients.
6. 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, some patients were not able to perform to the full extent of their physical abilities, due to the involvement of the patient’s ICD. We have only compared the OUES with the VO2peak so we can’t make assumptions about its relationship with VO2max. In other studies, they may also have used different methods to determine the VT1.

7. Conclusion

We can conclude that the OUES, an objectively derived and stable exercise parameter, correlates significantly with the VO2peak as well as with the VT1 in male and female patients with heart failure. The VO2peak and the VT1 also correlate significantly with each other.
8. References


9. Appendix

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

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

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 VO2 and VE during an incremental exercise. A. OUES, B. VO2/VE.

**Figure 2.** Relationship between the VO2peak and the OUES. $r=0.84$, $P<0.0001$. 
Figure 3. Relationship between the OUES and the VT1 (ml/min.) $r=0.81$, $p<0.0001$.

Figure 4. Relationship between the VO2peak(ml/min.) and the VT1 (ml/min.) $r=0.76$, $p<0.0001$. 
Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:

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
Jaar: 2016

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