ASSOCIATION OF CARDIO-PULMONARY STRESS TEST PARAMETERS AND HEART RATE RECOVERY IN OBESE SUBJECTS WITH OR WITHOUT TYPE II DIABETES

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ABSTRACT

Background and objectives: Heart rate recovery at first (HRR-I) and second (HRR-II) minute after exercise is accurate in estimating autonomic nervous system balance, and has been related to risk of cardiovascular events. Our aim was to determine independent predictors of HRR collected during standard cardio-pulmonary stress test (CPT) in a group of overweight/obese subjects without (N=14) and with type 2 diabetes (N=19), as compared to a sample (N=15) of healthy sedentary subjects.

Methods: A graded exercise test on treadmill was performed. Oxygen uptake at rest and at peak exercise (VO$_2$max), as well as respiratory exchange ratio at peak exercise was collected. Linear and logistic regression was used to assess association between variables collected at CPT and HRR-I and HRR-II.

Results: Age, gender, as well as VO2 and HR at rest were all comparable among groups. VO2max and HRmax were both lower in diabetic patients as compared to healthy and overweight/obese groups (20 ± 4.3 vs. 28 ± 7 vs. 25.1 ± 5 ml/kg/min respectively, p < 0.01). VO2max had the highest association to HRR-I (R$^2$=0.47) and HRR-II (R$^2$=0.44); VO2max < 28 and VO2max < 29 were the most accurate cut-off values to identify subjects with abnormally low HRR-I and HRR-II.

Conclusions: VO2max is an independent predictor of HRR-I or HRR-II, and it is able to discriminate between patients with normal or abnormally low HRR values. Further studies are warranted to test usefulness of a customized exercise program to ameliorate autonomic nervous system balance, therefore reducing global cardiovascular risk.

Key words: Cardio-Pulmonary Stress Test, Heart Rate Recovery, Autonomic Nervous System, maximal oxygen uptake (VO$_2$max).

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Introduction

Heart rate recovery (HRR) is the rate at which heart rate decreases, usually within minutes, after moderate to heavy exercise, and is regulated by autonomic nervous system$^{(1)}$. HRR immediately after exercise is a marker of parasympathetic function that has been shown to be inversely associated with insulin resistance, metabolic syndrome, and type 2 diabetes$^{(2)}$. Reduced HRR following maximal exercise testing is an important predictor of mortality in healthy adults$^{(3)}$, in patients with cardiovascular disease$^{(4)}$ and with diabetes$^{(5)}$.

The recent “Look AHEAD” study$^{(6)}$ suggested that lifestyle intervention aimed to improve cardiovascular fitness, defined as the estimated metabolic equivalent level based on the treadmill work load, has a beneficial effect upon autonomic nervous system function as reflected in the improvement of heart rate recovery after exercise in adults with type 2 diabetes. However, that study did not analyze changes in maximal oxygen consumption (VO2max), which is considered the best measure of overall cardiorespiratory fitness and an important predictor of cardiovascular and all-cause mortality$^{(7)}$, and its relationship with HRR.
Previous studies have shown that HRR is related to \( VO_2 \text{max} \) in athletes\(^8,9,10\), but to our knowledge there are few studies that compare changes in \( VO_2 \text{max} \) in overweight and obese patients with or without type II. Finally, no evidence exists of a possible association between \( VO_2 \text{max} \) and HRR in the heretofore mentioned population. Therefore, our aims in current study were twofold: to test relation between different measurements obtained by cardio-pulmonary stress and heart rate recovery, and to depict independent predictors of abnormal heart rate recovery detected at first or second minute in overweight and obese patients with or without type II diabetes as compared to a group of healthy sedentary subjects.

**Methods**

**Study population**

We prospectively enrolled a cohort of 48 consecutive subjects with no history of cardiovascular disease, cancer, or psychiatric or other major illness, who underwent complete cardio-pulmonary stress test at Sport and Exercise Sciences Research Unit (“DISMOT”) of our institution from February 1, 2010, through October 31, 2013. Overweight or obesity status has been detected by computation of the body mass index (BMI) \(^{(11)}\). Diagnosis of Type II Diabetes has been made according to the most recent American Diabetes Association guidelines\(^{(12)}\). Overweight/Obese or Diabetic/Obese subjects were compared to a sample of 15 sedentary but healthy subjects, with a BMI < 25 (control group).

Exclusion criteria were: known coronary artery disease, any grade of systemic hypertension, more than mild valve disease, current treatment with insulin or glitazones, any lung, muscular or general disability (i.e. peripheral vascular disease or arthropathy) preventing exercise test. None of recruited subjects had insulin resistance or family history for diabetes, and all subjects were non-smokers; none abused alcohol.

Finally, according to both symptoms and electrocardiographic monitoring, cardio-pulmonary stress test was negative for any signs of supra-ventricular or ventricular arrhythmias or myocardial ischemia for the whole study population recruited. All subjects included provided written informed consent to participate in the study. The procedures were conducted in compliance with the Declaration of Helsinki and were approved by the IRB Committee at our Institution.

**Cardio-pulmonary stress test**

All tests were performed between 8 and 10 a.m., after a 12-h overnight fast. Stature and body mass were measured before starting the tests using a stadiometer and an electronic weighing scale respectively (SECA, Germany). All subjects performed a graded exercise test to exhaustion on treadmill, according standard and modified Bruce protocols. A disposable facemask with a 50-80ml dead space (Cosmed V\(_2\), Cosmed Srl, Italy) was used to collect expired air throughout the test. Oxygen uptake (\( VO_2 \)) was recorded with a breath-by-breath measurement system (Cosmed Quark CPET, Cosmed Srl, Italy) and maximal oxygen uptake (\( VO_2 \text{max} \)) was defined as the highest consecutive 30-s average value achieved during the test. The flow meter and gas analyzers were calibrated before each test, according to the manufacturer’s instructions. Respiratory Exchange Ratio (RER) was defined as the ratio between the amount of \( CO_2 \) produced and \( O_2 \) consumed in one breath (determined from comparing exhaled gasses), and RER value reached at peak of exercise (peak RER) was collected.

During the tests standard 12-lead ECG was performed in all patients mainly for clinical monitoring (i.e. presence of arrhythmias or abnormalities of the ST-T tract), while the heart rate was accurately recorded using a short-range radio telemetry system (Polar Electro Oy, Finland). Finally, heart rate recovery (HRR) was defined as the difference between heart rate at peak exercise (HRmax) and heart rate 1 and 2 minutes after cessation of the exercise. The cool-down period after cessation of exercise consisted of walking on treadmill at 2.0 Km/h of speed and 0% of grade. All responses were monitored and graphically displayed throughout rest, exercise, and cool-down. The test was stopped when one or more of the following criteria were met: attainment of a \( VO_2 \text{max} \) plateau \(< 2.2 \text{ ml} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1} \); respiratory exchange ratio (RER) \(> 1.10 \); maximal heart rate (HR-max) close to theoretical value of 220-age; the subject was unable to maintain the required work rate.

**Statistical analysis**

Statistical analyses were performed with a commercially available software program (STATA v13.2; SAS Institute Inc, Cary, Texas). Comparisons between groups for continuous variables were made with the pair-wise nonparametric Wilcoxon rank sum test, and comparisons for cate-
gorical variables were performed using the Fisher exact test.

Simple (i.e. univariate) as well as multivari-
able Linear regression was used to depict indepen-
dent predictors of HRR-I and HRR-II (thus consid-
ered as continuous variables) among demographic,
biometric or measurements collected during CPT.

Multivariable linear regression final models were
built using a mixed stepwise strategy, with a
backward (possible independent predictors of HRR-
I and HRR-II were considered in the final multi-
variable model if their p-value at simple linear
regression was < 0.1) as well as a forward approach
(possible independent predictors of HRR-I and
HRR-II were considered in the final multivariable
model if their p-value at simple linear regression
was < 0.2). According to published evidence, we
further stratified patients basing on normal HRR at
first and second minute (HRR-I and HRR-II, ≥ 12
bpm or ≥ 24 bpm, respectively) or abnormally low
values (< 12 bpm and < 24 bpm for HRR-I and
HRR-II, respectively). Uni- as well as multivariable
Logistic regression and the derived ROC curves
were used to determine if a combination of cardio-
pulmonary parameters of cardiovascular perfor-
ance, including VO\textsubscript{2}max, HR at rest and at the
peak of the exercise, or Respiratory Ratio might be
a better discriminator than each index alone in iden-
tifying subjects with abnormal HRR-I (< 12 bpm)
or HRR-II (< 24 bpm) values, once age, gender, and
VO2 at rest were forced into the multivariable
model. Optimal cut-off values were defined by the
maximal Youden index (sensitivity + specificity -1).
Sensitivity, specificity, accuracy and positive and
negative predictive values were calculated by stan-
dard formulae. Regarding multivariable analysis,
the Akaike information criterion was employed to
define the best model fit by calculating the mini-
mum of -2 x log likelihood + 2 x k, where k repre-
sents the number of independent predictor vari-
ables.

Data are presented as mean ± SD, or number
(percentage). A difference was considered statisti-
cally significant if the P value was less than .05. In
the multivariate models, a variable was considered
a significant predictor of survival if the P value was
< 0.05.

## Results

### Demographic and cardio-pulmonary stress test characteristics among groups

A total of 48 subjects met the inclusion criteria
of current study. Of these, 15 subjects were healthy
sedentary (BMI < 25, Group I), 14 subjects were
classified as overweight or obese (Group II, 5
subjects with BMI > 25 but ≤ 30, classified as over-
weight, and 9 subjects with BMI > 30, classified as
obese). Finally, 19 subjects had a diagnosis of type
II diabetes (Group III, 9 of these diabetic patients
were also obese (BMI > 30), while 10 were over-
weight (BMI: 27.7 ± 1.4).

Age and gender distribution were comparable
among groups, while weight and BMI were higher
in overweight/obese and diabetic/obese as com-
pared to healthy subjects (Table 1). Beyond weight
and BMI, all collected variables at rest or during
CPT were similar between overweight/obese sub-
jects and healthy sedentary.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy Sedentary (N = 15)</th>
<th>Overweight/Obese (N = 14)</th>
<th>Diabetic/Obese (N = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>51 ± 6</td>
<td>52 ± 12</td>
<td>57 ± 7</td>
</tr>
<tr>
<td>Females (N (%))</td>
<td>8 (55)</td>
<td>7 (50)</td>
<td>11 (57)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 ± 9.2</td>
<td>168 ± 9.7</td>
<td>165 ± 7.2</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>62 ± 8.5</td>
<td>88 ± 10.8 §</td>
<td>86 ± 15 §</td>
</tr>
<tr>
<td>BMI</td>
<td>23 ± 1.5</td>
<td>31 ± 2.5 §</td>
<td>32 ± 6 §</td>
</tr>
<tr>
<td>VO\textsubscript{2}rest (ml/Kg/min)</td>
<td>3.8 ± 1.3</td>
<td>3.8 ± 1</td>
<td>3.7 ± 1.1</td>
</tr>
<tr>
<td>HRrest (bpm)</td>
<td>75 ± 13</td>
<td>71 ± 9.2</td>
<td>73 ± 12</td>
</tr>
<tr>
<td>VO\textsubscript{2}max (ml/Kg/min)</td>
<td>28 ± 7</td>
<td>25.1 ± 5</td>
<td>26 ± 4.3 §</td>
</tr>
<tr>
<td>VO\textsubscript{2}max (%)</td>
<td>86 ± 18</td>
<td>93 ± 15.7</td>
<td>84 ± 14.4</td>
</tr>
<tr>
<td>HRmax (bpm)</td>
<td>140 ± 17</td>
<td>143 ± 13</td>
<td>130 ± 16 Y</td>
</tr>
<tr>
<td>HRmax (%)</td>
<td>83 ± 9.5</td>
<td>85 ± 3.9</td>
<td>77 ± 8.8 §</td>
</tr>
<tr>
<td>Respiratory Exchange Ratio (Peak)</td>
<td>1.05 ± 0.1</td>
<td>1.05 ± 0.1</td>
<td>0.99 ± 0.1 §</td>
</tr>
<tr>
<td>HRR-I min (bpm)</td>
<td>24 ± 9</td>
<td>19 ± 8</td>
<td>17 ± 6 F</td>
</tr>
<tr>
<td>HRR-I &lt; 12 bpm (N (%))</td>
<td>2 (13)</td>
<td>3 (21)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>HRR-II min (bpm)</td>
<td>37 ± 12</td>
<td>34 ± 10</td>
<td>28 ± 8 F</td>
</tr>
<tr>
<td>HRR-II &lt; 24 bpm (N (%))</td>
<td>3 (21)</td>
<td>3 (21)</td>
<td>5 (26)</td>
</tr>
</tbody>
</table>

\( \S = p < 0.05 \) vs Healthy \( \Delta = p < 0.01 \) vs Healthy
\( \P = p < 0.001 \) vs Healthy
\( \Y = p < 0.05 \) vs Overweight/Obese
\( \Y = p < 0.01 \) vs Overweight/Obese
\( \Y = p < 0.001 \) vs Overweight/Obese

### Table 1: Demographic characteristics and Cardio-
Pulmonary stress test (CPT) measurements in the popu-
lation under study. Descriptions are with mean ± stand-
ard deviation, or count (percent).
VO₂ and heart rate collected in resting conditions were also similar among the groups, while VO₂ and heart rate reached at peak exercise (VO₂max and HRmax, respectively) were both lower in diabetic patients as compared to overweight/obese and healthy subjects. Likewise, peak RER, as well as HRR detected at I, and II minute were all lower in diabetic patients as compared to the other 2 groups. Diabetic patients had also the highest prevalence of abnormally low HRR-I and HRR-II, although difference was not statistically significant. Of note, Independently from BMI value or presence of diabetes, males had on average higher VO₂max as compared to females (26.8 ± 5.4 vs 21.6 ± 6.3 ml/Kg/min, respectively, p = 0.003), while both heart rate at rest and heart rate at peak exercise were comparable between males and females (p = 0.41 and p=0.74, respectively).

**Linear regression analysis**

**Predictors of HRR-I by Univariate and Multivariable Linear Regression**

Considering all enrolled subjects together, age was significantly and negatively related to HRR-I, although the predictive value was low (R² = 0.16, Table 2). VO₂max or HRmax either considered as absolute value or as percentage of the predicted value were all positively related to HRR-I with VO₂max showing the highest predictive power (R² = 0.47, Table 2). According to stratified analysis, relation between VO₂max and HRR-I was confirmed in healthy sedentary subjects and in diabetic (obese) patients, while it was not anymore significant in overweight/obese group. Peak RER was a significant positive predictor of HRR-I only in diabetic patients, although predictive value was low (R² = 0.19).

According to multivariable analysis, VO₂max was confirmed as independent and positive predictor of HRR-I (Table 3). Besides, male gender, overweight/obese status, and having higher heart rate at rest were all predictors of lower HRR-I values.

**Predictors of HRR-II by univariate and multivariable linear regression**

Considering all subjects together, age was confirmed as a predictor of HRR-II, with a negative relation (Table 2). Similarly to HRR-I, VO₂max, HRmax, VO₂max (%) and HRmax (%) were all predictors positively related to HRR-II, with VO₂max showing the greatest predictive value (R² = 0.44). According to multivariable analysis, age, gender, heart rate at rest, and VO₂max were all independently related to HRR-II values (Table 3).

**Logistic Regression and ROC Analysis**

**Predictors of Normal/Abnormal HRR-I by ROC analysis and Univariate and Multivariable Logistic Regression**

Stratifying patients according to normal/abnormal HRR-I value (≥ 12 and <12 bpm, respectively), VO₂max was the most accurate measurement to discriminate subjects with normal or abnormally low HRR-I, irrespective of BMI or diabetes (AUC 0.80, 95% CI 0.67 - 0.86) (table 4). According to ROC analysis, the cut-off value with highest accuracy to identify subjects with HRR-I < 12 bpm was a VO₂max ≤ 28 ml/Kg/min (Positive predictive value: 67%, negative predictive value: 84%) (table 4). Consistently, univariate logistic regression confirmed results obtained by ROC analysis, showing that subjects with higher VO₂max had a greater probability of normal HRR-I (i.e. HRR-I ≥ 12 bpm), with an odds ratio of 0.78 (table 4).

According to multivariable logistic regression, VO₂max was the only independent predictor of normal/abnormal HRR-I with subjects with the greatest VO₂max at the lowest risk of having an abnormally low HRR-I (p = 0.01) (Table 5).

**Predictors of Normal/Abnormal HRR-II by ROC analysis and Univariate and Multivariable Logistic Regression**

Consistently with HRR-I prediction, higher VO₂max was predictive of normal HRR-II (i.e. ≥ 24 bpm) as well, and was able to correctly identify subjects with abnormally low HRR-II in 71% of the cases. The cut-off value with the highest accuracy was a VO₂max ≤ 29 ml/Kg/min (positive predictive value: 50%, Negative predictive value: 80%) (table 4). Moreover, the higher the heart rate at rest, the greater the chance to have an abnormally low HRR-II (i.e. < 24 bpm, OR = 1.08).

According to multivariable analysis, heart rate at rest was the only significant predictor of normal/abnormal HRR-II, while VO₂max was only marginally significant (p = 0.08) (table 5).
<table>
<thead>
<tr>
<th>Variable</th>
<th>All Enrolled Subjects</th>
<th>Healthy Sedentary</th>
<th>Overweight/Obese</th>
<th>Diabetic/Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^2 (β ± SD))</td>
<td>(N = 48)</td>
<td>(N = 15)</td>
<td>(N = 14)</td>
<td>(N = 19)</td>
</tr>
<tr>
<td>HRR-I min (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>0.16 (-0.38 ± 0.13)**</td>
<td>0.12 (-0.21 ± 0.16)</td>
<td>0.16 (-0.56 ± 0.37)</td>
<td>0.1 (-0.37 ± 0.27)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.05 (0.22 ± 0.14)</td>
<td>0.15 (0.37 ± 0.23)</td>
<td>0.01 (0.12 ± 0.33)</td>
<td>0.16 (0.48 ± 0.27)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>0.04 (-0.1 ± 0.07)</td>
<td>0.1 (0.28 ± 0.24)</td>
<td>0.06 (0.31 ± 0.36)</td>
<td>0.05 (-0.56 ± 0.59)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.11 (-0.48 ± 0.2)*</td>
<td>0.00 (0 ± 0.04)</td>
<td>0.06 (0.07 ± 0.08)</td>
<td>0.15 (-0.39 ± 0.22)</td>
</tr>
<tr>
<td>VO_{2rest} (ml/Kg/min)</td>
<td>0 (0.3 ± 1.09)</td>
<td>0.00 (-0.01 ± 0.04)</td>
<td>0.06 (-0.03 ± 0.03)</td>
<td>0.14 (0.07 ± 0.04)</td>
</tr>
<tr>
<td>HRrest (bpm)</td>
<td>0.09 (-0.22 ± 0.1)</td>
<td>0.26 (-0.7 ± 0.33)*</td>
<td>0.13 (-0.39 ± 0.5)</td>
<td>0.03 (-0.15 ± 0.48)</td>
</tr>
<tr>
<td>VO_{2max} (ml/Kg/min)</td>
<td>0.47 (0.69 ± 0.16)**</td>
<td>0.25 (0.37 ± 0.18)*</td>
<td>0.03 (0.1 ± 0.17)</td>
<td>0.48 (0.5 ± 0.13)**</td>
</tr>
<tr>
<td>VO_{2max} (%)</td>
<td>0.37 (0.17 ± 0.07)**</td>
<td>0.44 (1.27 ± 0.39)**</td>
<td>0.01 (-0.14 ± 0.54)</td>
<td>0.16 (0.94 ± 0.53)</td>
</tr>
<tr>
<td>HRmax (bpm)</td>
<td>0.22 (0.18 ± 0.07)**</td>
<td>0.16 (0.74 ± 0.47)</td>
<td>0.02 (0.21 ± 0.43)</td>
<td>0.14 (0.96 ± 0.59)</td>
</tr>
<tr>
<td>HRmax (%)</td>
<td>0.20 (0.22 ± 0.14)*</td>
<td>0.13 (0.37 ± 0.26)</td>
<td>0.13 (-0.16 ± 0.12)</td>
<td>0.04 (0.28 ± 0.35)</td>
</tr>
<tr>
<td>Respiratory Exchange Ratio Peak</td>
<td>0.01 (8.09 ± 13.97)</td>
<td>0.04 (0.00 ± 0.00)</td>
<td>0.00 (0.00 ± 0.00)</td>
<td>0.19 (0.00 ± 0.00)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Enrolled Subjects</th>
<th>Healthy Sedentary</th>
<th>Overweight/Obese</th>
<th>Diabetic/Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRR-II min (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Years)</td>
<td>0.22 (-0.57 ± 0.16)**</td>
<td>0.12 (-0.17 ± 0.13)</td>
<td>0.40 (-0.74 ± 0.26)*</td>
<td>0.06 (-0.21 ± 0.2)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.04 (0.26 ± 0.18)</td>
<td>0.07 (0.2 ± 0.2)</td>
<td>0.01 (0.11 ± 0.28)</td>
<td>0.14 (0.33 ± 0.2)</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>0.01 (-0.07 ± 0.09)</td>
<td>0.05 (0.15 ± 0.19)</td>
<td>0.13 (0.39 ± 0.29)</td>
<td>0.01 (-0.15 ± 0.44)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.06 (-0.44 ± 0.27)</td>
<td>0 (0 ± 0.03)</td>
<td>0.2 (0.11 ± 0.06)</td>
<td>0.06 (-0.18 ± 0.17)</td>
</tr>
<tr>
<td>VO_{2rest} (ml/Kg/min)</td>
<td>0 (-0.05 ± 1.38)</td>
<td>0 (0 ± 0.03)</td>
<td>0.09 (-0.03 ± 0.03)</td>
<td>0.04 (0.03 ± 0.03)</td>
</tr>
<tr>
<td>HRrest (bpm)</td>
<td>0.09 (-0.27 ± 0.13)</td>
<td>0.29 (-0.58 ± 0.25)*</td>
<td>0.06 (-0.22 ± 0.26)</td>
<td>0.03 (-0.25 ± 0.35)</td>
</tr>
<tr>
<td>VO_{2max} (ml/Kg/min)</td>
<td>0.44 (0.92 ± 0.2)**</td>
<td>0.36 (0.35 ± 0.13)*</td>
<td>0.01 (0.04 ± 0.14)</td>
<td>0.37 (0.32 ± 0.1)*</td>
</tr>
<tr>
<td>VO_{2max} (%)</td>
<td>0.27 (0.26 ± 0.09)**</td>
<td>0.59 (1.14 ± 0.27)**</td>
<td>0.04 (-0.31 ± 0.45)</td>
<td>0.22 (0.83 ± 0.37)*</td>
</tr>
<tr>
<td>HRmax (bpm)</td>
<td>0.21 (0.29 ± 0.09)**</td>
<td>0.24 (0.71 ± 0.35)*</td>
<td>0.16 (0.51 ± 0.34)</td>
<td>0.08 (0.55 ± 0.44)</td>
</tr>
<tr>
<td>HRmax (%)</td>
<td>0.12 (0.43 ± 0.17)**</td>
<td>0.21 (0.36 ± 0.19)</td>
<td>0.05 (-0.07 ± 0.11)</td>
<td>0.07 (0.27 ± 0.25)</td>
</tr>
<tr>
<td>IR Peak</td>
<td>0.04 (23.32 ± 17.45)</td>
<td>0.14 (0 ± 0)</td>
<td>0.01 (0 ± 0)</td>
<td>0.16 (0 ± 0)</td>
</tr>
</tbody>
</table>

* = p-value < 0.05 for selected predictor
** = p-value < 0.01 for the selected predictor

Table 2: Simple (i.e. univariate) linear regression analysis of heart rate recovery at first minute and second minute after exercise (HRR-I and HRR-II, respectively, dependent variables) on collected demographic measures and CPT values (considered as independent variables or predictors). * = p-value < 0.05 ** = p-value < 0.01.
Irrespective of BMI values or type II diabetes. Abnormally low HRR-I (< 12 bpm) or HRR-II (< 24 bpm), ≥ or normal HRR-II (≥ 12 bpm) as opposed to subjects with ≥ 12 bpm),

Receiver-Operator Curves (ROC) analysis to detect predictive power of collected demographic and CPT measurements to the outcome variable is HRR-I (Table 4a) and HRR-II (Table 4b). The most promising models were selected according to the Aka-Ike Index.

Independent Predictors of HRR-I min (continuous var.)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N = 48</th>
<th>Predictor</th>
<th>N = 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.28</td>
<td>Age (years)</td>
<td>0.47</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>-4.4</td>
<td>Gender (males)</td>
<td>-1.7</td>
</tr>
<tr>
<td>Group (overweight-obese)</td>
<td>-0.8</td>
<td>HRrest (bpm)</td>
<td>0.07</td>
</tr>
<tr>
<td>VO2max (ml/Kg/min)</td>
<td>0.66</td>
<td>VO2max (ml/Kg/min)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Table 3: Stepwise multivariable linear regression models. Continuous predictor = p-value 0.05

**Table 4**: Simple (i.e. univariate) logistic regression and Receiver-Operator Curves (ROC) analysis to detect predictive power of collected demographic and CPT measurements to discriminate between subjects with normal HRR-I (≥ 12 bpm) or normal HRR-II (≥ 24 bpm) as opposed to subjects with abnormally low HRR-I (< 12 bpm) or HRR-II (< 24 bpm), irrespective of BMI values or type II diabetes.

Discussion

To our knowledge this is the first study that puts in relation measures detected at cardio-pulmonary stress test to predict HRR in heterogeneous groups of non athletes, overweight/obese subjects with or without diabetes.

During exercise there is activation of the sympathetic nervous system and withdrawal of parasympathetic activity; the reverse occurs during recovery. Heart rate recovery is mediated by vagal reactivation, and the rate at which HR declines appears to be a reflection of a faster recovery from the sympathetic drive necessary during exercise(13).

A faster HRR may therefore be a function of increase in vagal activity or reduction in sympathetic activity. Kannankeril et al. (14) analyzed heart rate in 10 healthy individuals during peak exercise and recovery under normal physiological conditions as well as during selective parasympathetic blockade with atropine. Upon cessation of exercise, augmentation of parasympathetic effects on HR occurred rapidly within the first minute. The Intensity of parasympathetic reactivation steadily increased further until 4 min into recovery, after which time parasympathetic effects on HR remained relatively constant. These data suggest that early HRR after exercise is predominantly due to parasympathetic reactivation, with sympathetic and non autonomic components probably playing lesser roles.

Dixon et al. and Du et al. (15, 16) demonstrated this fact when they found that athletes, who had higher vagal activity and lower sympathetic activity, had faster HRR than non-athletes. Similarly, Imai et al. (13) in a study involving 20 patients with chronic heart failure and 9 athletes found that vagally mediated HRR after exercise is accelerated in well trained athletes but blunted in patients with chronic heart failure.

Consistently with previous reports, age was inversely related to both HRR-I and HRR-II even in our population, irrespective of BMI or diabetes(17).

Furthermore, several reports have also highlighted the direct relation between maximum oxygen consumption (VO2max) and HRR (2, 16, 18). However, these findings have been observed primarily on highly trained athletes, and no data compare sedentary, middle age subjects with nor-
normal BMI, or overweight/obese, to patients with type II diabetes and overweight/obese as well.

In other words, subjects with better functional capacity (by VO$_2$\textsubscript{max}) have also greater chances to have normal HRR. This is consistent with previous observations highlighting role of HRR-I and HRR-II to depict risk of cardiovascular diseases in an extensive unselected population of apparently healthy subjects undergoing cardio-pulmonary stress test\(^{(3)}\).

It is also noteworthy the positive relation between heart rate detected at peak exercise and HRR: based on the model proposed by Rosenblueth and Simeone\(^{(19)}\), heart rate is a simple measure which can provide an index of the net effects of sympathetic and parasympathetic inputs to the sinus node, so it is perhaps not surprising that peak heart rate is related to HRR. Interestingly, this relation was significant only considering the whole population, was mainly driven by the healthy sedentary group and was definitely not significant in overweight/obese diabetic patients, those who reached the lowest values of peak heart rate as well as the lowest expected heart rate at peak exercise.

According to multivariable linear regression, heart rate at rest was inversely related to HRR-I and HRR-II values (the relation was marginally significant) irrespectively of age, gender or group. This observation is probably related to global cardiopulmonary fitness of our population: subjects with higher HR at rest have also worse cardiopulmonary fitness, have lower HRR-I and HRR-II (and, consequently, higher risk of developing cardiovascular diseases in the future).

It is more difficult to explain why males have a significantly lower predicted HRR-I or HRR-II. Significant relationship between gender and HRR has been already reported\(^{(20)}\), and has been ascribed to a reduced heart rate reserve (i.e. the difference between heart rate at peak exercise and heart rate at rest) in females as compared to males. However, in our study males and females had similar HR either at rest or at peak exercise, so that HR reserve must be similar as well. Furthermore, gender becomes a significant predictor of HRR only after correction for VO$_2$\textsubscript{max}: in other words males in our population have lower HRR-I and HRR-II (and, consequently, higher risk of developing cardiovascular diseases in the future).

In our study, diabetic patients (and also overweight/obese) had lower VO$_2$\textsubscript{max}, HR\textsubscript{max}, peak RER as well as HRR-I and HRR-II as compared to overweight/obese non diabetic patients or controls. We have confirmed that VO$_2$\textsubscript{max} is the parameter with the highest predictive accuracy of HRR-I and HRR-II after exercise, able to identify subjects with abnormally low HRR as well. Interestingly, this relationship is most significant in healthy sedentary subjects and still true on overweight/obese diabetic patients, but was blunted and was not significant anymore in non diabetic subjects with BMI > 25, at either first or second minute after exercise. Surprisingly, according to the expected VO$_2$\textsubscript{max} (in percentage) our group of overweight/obese non diabetic subjects had also the best performance as compared to either healthy sedentary subjects or overweight/obese diabetic patients.

Unfortunately, we did not perform a direct assessment of autonomic nervous system in our population, thus we can just speculate that another and unmeasured factor influences relationship between VO$_2$\textsubscript{max} and HRR in overweight/obese subjects. This relationship is not present in diabetic patients with a comparable BMI. However, irrespective to BMI, diabetes, and resting heart rate and VO$_2$, VO$_2$\textsubscript{max} was the only significant and accurate measurement to identify subjects with an abnormally low HRR at both first and second minute.

### Table 5: Stepwise multivariable logistic regression models

Categorical outcome variable is HRR-I (> 12 bpm vs ≤ 12 bpm, table 5a) and HRR-II (> 24 bpm or < 24 bpm). The models were built with a stepwise (mixed, forward and backward) approach, and age, gender as well as VO2 at rest were forced into the model to test independent predictive power of VO$_2$\textsubscript{max}.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (Stand Err)</th>
<th>p-value</th>
<th>Predictor</th>
<th>Odds Ratio (Stand Err)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.05 (0.12)</td>
<td>0.63</td>
<td>Age (years)</td>
<td>1.11 (0.10)</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>4.97 (6.6)</td>
<td>0.23</td>
<td>Gender (males)</td>
<td>0.84 (0.91)</td>
<td>0.8</td>
</tr>
<tr>
<td>HR\textsubscript{rest} (bpm)</td>
<td>1.16 (0.10)</td>
<td>0.08</td>
<td>HR\textsubscript{rest} (bpm)</td>
<td>1.14 (0.07)</td>
<td>0.03 *</td>
</tr>
<tr>
<td>VO$_2$\textsubscript{rest} (ml/Kg/min)</td>
<td>1.66 (0.86)</td>
<td>0.33</td>
<td>VO$_2$\textsubscript{rest} (ml/Kg/min)</td>
<td>1.35 (0.60)</td>
<td>0.51</td>
</tr>
<tr>
<td>VO$_2$\textsubscript{max} (ml/Kg/min)</td>
<td>0.59 (0.12)</td>
<td>0.01 **</td>
<td>VO$_2$\textsubscript{max} (ml/Kg/min)</td>
<td>0.82 (0.09)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

N = 48
Limitations

Main limitation of our study is the pretty low sample size. However, we have been able to show significant differences among groups, and several predictors of HRR at both the first and second minute. Another limiting factor is the lack of an extensive assessment of autonomic nervous system in our population. However, HRR has been already validated as an important surrogate of such performance, and we have collected an extensive set of parameters obtained at cardio-pulmonary stress test on an unprecedented population of sedentary subjects, with normal BMI, overweight/obese, with or without diabetes.

Conclusions

In this study we have compared key measures of functional capacity among healthy sedentary subjects, sedentary overweight/obese patients with and without type II diabetes, to identify possible predictors of HRR. VO_{2\text{max}} was the single most significant and independent positive predictor of HRR, detected at first and second minute after exercise. Moreover, after correcting for VO_{2\text{max}}, being a male and having higher heart rate at rest predicted subjects with lower HRR values. These observations relate cardiopulmonary fitness to autonomic nervous system efficiency assessed by HRR in non-athletes. Since lower HRR has been demonstrated as a negative prognostic factor of cardiovascular events, our reports highlights the critical importance of a well balanced exercise program to ameliorate autonomic imbalance and reduce global cardiovascular risk.

References

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