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**Does Genetic Variation in *PPARGC1A* Affect Exercise-Induced Changes in Ventilatory Thresholds and Metabolic Syndrome?**

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**ABSTRACT**

**Ring-Dimiriou S, Kedenko L, Kedenko I, Feichtinger RG, Steinbacher P, Stoiber W, Foerster H, Felder T, Mueller E, Kofler B, Paulweber B.** Does Genetic Variation in *PPARGC1A* Affect Exercise-Induced Changes in Ventilatory Thresholds and Metabolic Syndrome? **JEPonline**2014;17(2):1-18. It has been demonstrated that single nucleotide polymorphism (SNP) in the peroxisome proliferator-activated receptor- coactivator-1** gene (*PPARGC1A,* rs8192678, G/A) affect the exercise-induced change in maximal oxygen uptake (VO2). However, studies investigating the effect of this SNP on submaximal exercise performance markers are quite sparse. Therefore, we investigated the effect of a 10-wk supervised cycling training (3x 60 min·wk-1) on VO2 and work rate at the point of optimal ventilatory efficiency (POE), anaerobic threshold (ANT), respiratory compensation point (RCP), and maximum level in subjects with different genotypes in PPARGC1A. Analyses were completed in 24 untrained men aged 58 ± 6 yrs. Regarding genotype (G/A; Gly482Ser), three groups were formed (3x n=8): GT1 (G/G, wild type, common allele frequency); GT2 (A/A, homozygous); and GT3 (G/A, heterozygous). Before and after the exercise intervention blood samples and body composition in the fasted state were tested, and an incremental cycle ergometer test (10 W·min-1) until volitional exhaustion with measurements of respiratory gas exchange and heart rate were completed. In sum, the occurrence rate of metabolic syndrome was not affected by genotype or short-term supervised cycling. Ten weeks of cycling at 80-100% ANT and 90-120% RCP improved VO2 and work rate at POE and RCP significantly. Furthermore, repeated ANOVA revealed a significant interaction between genotype and exercise with the highest responder in GT1 compared to GT3 and GT2. The results of this prospective study point towards the hypothesis that the SNP rs8192678 affects the trainability of aerobic capacity measured as VO2 or work rate at RCP of previously untrained middle-aged men.

**Key Words**: *PPARGC1A*, Exercise-Induced Trainability, Untrained Adults

**INTRODUCTION**

One primary goal of exercise intervention is the improvement of cardiorespiratory fitness (i.e., VO2 max), which is associated with a reduced all-cause mortality rate, a reduction in cardiopulmonary and/or metabolic disorders, as well as an improvement in the health of subjects with chronic diseases and those prone to the metabolic syndrome (MetS) ([5](#_ENREF_5),[22](#_ENREF_22),[24](#_ENREF_24),[40-42](#_ENREF_40)). However, what is interesting when assessing individual responses to regular exercise is that healthy untrained adults display a large inter-individual variation in VO2 max that ranges from -20% to +50% ([6](#_ENREF_6),[16](#_ENREF_16),[41](#_ENREF_41)).

The observed differences in the training effect may be partly explained by the dissimilarities in study population. Other considerations include the exercise prescription, duration of exercise intervention, and genetic factors ([6](#_ENREF_6),[46](#_ENREF_46)). As to the latter factor, Bouchard (5) indicates that the exercise-induced variation in VO2 max is 47% explained by heritability ([5](#_ENREF_5)). Recently, the genetic variations of the deoxyribonucleic acid (DNA) sequence of certain genes have been included when studying exercise-induced training effects ([1](#_ENREF_1),[18](#_ENREF_18),[28](#_ENREF_28),[29](#_ENREF_29" \o "Maciejewska, 2012 #2078)). The replacement of single nucleotides, known as single nucleotide polymorphisms (SNP), are the most common type of genetic variation ([43](#_ENREF_43)).

In the present study, we focused on the SNP rs8192678 (G/A, Gly482Ser) of the gene peroxisome proliferator-activated receptor- coactivator-1 (*PPARGC1A*). This gene encodes the protein PGC-1, which is a key co-activator of several nuclear transcription factors. It is a master regulator of mitochondrial biogenesis, mitochondrial respiration, skeletal muscle fiber transformation (from fast to slow twitch), glucose and fatty acid metabolism, and the anti-oxidation machinery ([4](#_ENREF_4),[21](#_ENREF_21),[35](#_ENREF_35),[38](#_ENREF_38),[42](#_ENREF_42),[48](#_ENREF_48)). *PPARGC1A* is expressed in cell types with high oxidative function (i.e., heart, skeletal muscle slow-twitch fibers, liver, and pancreas) and in brown adipose tissue ([49](#_ENREF_49),[50](#_ENREF_50)). In this context, exercise can serve as a stressor that increases the expression of *PPARGC1A* via adenosine-monophosphate kinase and sirtuin-1 ([8](#_ENREF_8),[21](#_ENREF_21)).

Recently, it has been reported that the endurance trained phenotype (cyclists) showed significantly higher messenger ribonucleic acid (mRNA) expression in *PPARGC1A* compared to healthy active but untrained phenotype, sedentary inactive and spinal cord injured subjects ([23](#_ENREF_23)). In addition, a significant increase in *PPARGC1A* expression was found after 3 hrs cycling in young healthy subjects ([13](#_ENREF_13)). Beside the impact of exercise, it has been demonstrated that overweight healthy subjects with no family history of type-2 diabetes mellitus (T2D) were characterized by a significantly higher expression in *PPARGC1A* compared to a matched sample with a family history of T2D and to subjects with manifest T2D ([36](#_ENREF_36)).

Several studies have shown that SNPs in *PPARGC1A* are associated to a significant lower level in aerobic power (i.e., VO2 max) in insulin resistant and untrained individuals as well as in athletes ([1](#_ENREF_1),[28](#_ENREF_28), [29](#_ENREF_29),[51](#_ENREF_51),[53](#_ENREF_53)). To date only one study (51) has investigated the effect of an exercise intervention on insulin sensitivity and aerobic capacity (i.e., %VO2 max at submaximum level) in subjects with the point mutation rs8192678 in the *PPARGC1A* gene. The data revealed that 9 months of regular exercise caused an insufficient training response in insulin sensitivity and in VO2 at the anaerobic threshold (ANT) in adults carrying the rare allele in *PPARGC1A* while subjects who were homozygous for the common allele showed a significant increase in insulin sensitivity and VO2 at the ANT ([51](#_ENREF_51)).

The ANT is a submaximal marker of oxidative capacity, characterizing the individual’s performance level where a transition from a predominantly aerobic to partially anaerobic energy metabolism occurs (VT1). Beside the ANT, the point of optimal ventilatory efficiency (POE) should also be used since it represents the work rate that is fully covered by aerobic energy supply. This point was described by Hollmann (1959) as another approach to measure VT1 since differences were found in work rate at POE compared to ANT ([3](#_ENREF_3),[14](#_ENREF_14),[16](#_ENREF_16),[20](#_ENREF_20),[33](#_ENREF_33),[52](#_ENREF_52),[58](#_ENREF_58),[60](#_ENREF_60)). The transition from a partially anaerobic to predominantly anaerobic energy consumption indicates a second inflection point (VT2) in incremental pulmonary exercise testing ([3](#_ENREF_3),[47](#_ENREF_47),[60](#_ENREF_60)). This point is often called the respiratory compensation point (RCP, VT2). The RCP equals the work rate where the end-tidal pressure of carbon dioxide (PETCO2) begins to decline after isocapnic buffering to compensate for metabolic acidosis ([3](#_ENREF_3),[9](#_ENREF_9),[11](#_ENREF_11),[33](#_ENREF_33),[45](#_ENREF_45),[54](#_ENREF_54),[56](#_ENREF_56), [58](#_ENREF_58),[60](#_ENREF_60)).

Despite the apparent impact of the aforementioned gene variant on the regulation of the skeletal muscle metabolism, there is a lack of prospective studies investigating the effect of SNPs on markers of the oxidative capacity and the MetS in untrained subjects. Therefore, the primary aim of the study was to test the hypothesis, that untrained men who are homozygous or heterozygous carriers of the rare allele in *PPARGC1A* will show a reduced change in oxygen uptake and work rate at submaximal performance level compared to men characterized by the common genotype after 10 wks of endurance exercise. We also investigated the effect of genotype on the occurrence rate of the MetS, and tested the comparability of the three ventilatory thresholds as markers of aerobic capacity.

**METHODS**

**Subjects and Group Assignment**

For the prospective 10 wks of exercise intervention, 838 males of a study cohort (SAPHIR, ([44](#_ENREF_44))) were genotyped for the SNP rs8192678 in the gene *PPARGC1A*. The criteria for exclusion of individuals included: (a) manifest T2D; (b) anti-diabetic and/or anti-coagulation medications; (c) extreme diet (i.e., very-low carbohydrate diet); and (d) surgery within the last 6 months prior to the onset of the study. One or more of these factors may have affected the outcome in the investigation (i.e., blood samples, exercise performance). Distance to testing and exercise locations led to further loss of individuals, resulting in a sample size of 44 subjects who met the following inclusion criteria: (a) untrained (≤1 hr·wk-1 sport activity); and (b) between 45 to 65 yrs of age. All subjects were informed verbally about the purpose of the study, the testing procedures, risks, and exercise intervention. The study was approved by the local ethics committee (E1243, 2010-10-04).

Due to several medical problems not associated with the exercise training program that included time constraints (compliance of <80% sessions completed) and missing gas-exchange or clinical data, the final sample consisted of 24 subjects representing three genotype groups. Based on SNP analysis (rs8192678), 8 subjects carried the common allele in *PPARGC1A* (G/G) and were defined as genotype 1 (GT1), 8 men were homozygous (GT2), and 8 subjects were heterozygous (G/A) of the rare allele(GT3).

**Genotyping**

Genomic DNA was isolated from whole blood by standard procedures (Puregene Kit, Gentra, MN, USA) from all subjects of the SAPHIR population and stored at -20˚C. Genotyping for SNP (rs8192678) was performed by the TaqMan SNP allelic discrimination method using an ABI 7900HT instrument (Applied Biosystems, Foster City, CA, USA) and pre-designed TaqMan SNP genotyping assays from Applied Biosystems (Foster City, CA, USA). A total of 5% of samples were genotyped in duplicate to ensure concordance. Genotype frequencies were tested for compatibility with Hardy-Weinberg equilibrium (HWE) using chi-square (**2) test (P≤0.05).

**Assessment of Metabolic Syndrome (MetS)**

Using the definition (2) of the International Diabetes Federation (IDF), subjects were characterized with MetS if they had central obesity measured by a waist circumference ≥102 cm plus 2 of 4 additional factors such as an increase in fasting plasma glucose (FPG ≥100 mg·dL-1) or previously diagnosed T2D, raised triacylglycerol level (TG ≥150 mg·dL-1), reduced high-density lipoprotein cholesterol level (HDL-C <40 mg·dL-1) or specific medical treatment for lipid abnormalities, and raised systolic and/or diastolic blood pressure (SBP ≥130 mmHg / DBP ≥85 mmHg) or previously diagnosed hypertension.

One week before the first exercise session baseline ambulatory SBP and DBP of the day-phase were measured via Riva Rocci method (Boso Rapid Manometer, Bosch and Son, Germany) and 10 mL blood was collected from the anticubital vein after an overnight fast to assess blood measures. All blood samples were coded and subsequently assayed blinded. FPG was measured using the glucose oxidase method and inter-assay coefficient of variation (CV) was calculated to be 1.7% for the applied method. Based on a turbidimetric measurement after agglutination of the antigen-antibody complex (Tina-quant method, Roche Diagnostics, Austria) the concentrations of HDL-C (CV 1.85%) and TG (CV 1.8%) were assessed.

**Anthropometric Characteristics and Body Composition**

Body height and body mass (BM, kg) were measured barefoot in a standing position wearing light clothing by utilizing a standard balance and scale (SECA 715, Vogel and Halke, Hamburg, Germany). From both measures the body mass index (BMI) was calculated to identify the overweight (BMI ≥25 to 29.9 kg·m-2) and obese (BMI of 30 to 39.9 kg·m-2) subjects according to the World Health Organization ([59](#_ENREF_59)). Regional body fat was determined by measuring the waist circumference 0.5 cm below the umbilicus with a standardized spring-loaded elastic tape (Roche, Mannheim, Germany) in the standing upright position with the feet 20 to 30 cm apart to determine the main characteristic of the MetS ([26](#_ENREF_26)). Lean body mass (LBM, kg) and body fat (BF, kg) were estimated by multi-frequency bio-impedance analysis (B.I.A. Nutriguard-M, Data Input, Darmstadt, Germany). Electrodes (BIANOSTIC) were attached on the frontal site of the right wrist and ankle of the subject lying in supine position. The recording started after 5 min of rest according to the manufactures guidelines (Data Input, Darmstadt, Germany).

**Exercise Testing and Assessment of Ventilatory Thresholds**

Exercise testing was completed within the same hour pre- and post-cycling training. Prior to each exercise test, each subject was instructed to abstain from sport activities 48 hrs, eating and drinking 3 hrs before testing. A ramp test protocol using an electronically-braked cycle ergometer (Ergoselect 100, Ergoline, GER) with 10-W increments per minute (60-70 rev·min-1) was conducted to determine ventilatory thresholds and peak oxygen uptake (VO2peak) ([7](#_ENREF_7),[45](#_ENREF_45),[57](#_ENREF_57)). Each subject started with a warm-up, cycling at 50 W for 4 min. Volitional fatigue was attained and defined by the following criteria: 90% of age-adjusted maximum heart rate (220-age), VO2peak change ≤2 mL·kg-1·min-1 with increasing load, and ≥1.1 respiratory exchange ratio. Dependent on the protocol VO2peak was assessed in the last stage as the mean value of 5 consecutive breaths with the 3rd breath including the maximal VO2-value.

Gas exchange analysis was conducted in breath-by-breath mode to measure minute ventilation (VE), breathing frequency (B*f*), gas concentration of oxygen (VO2), and carbon dioxide production (VCO2) (ZAN 600, nSpire Health GmbH, CO, USA). The inspired and expired air flow were continuously measured with a pneumotachograph (VIPTM, nSpire Health GmbH, CO, USA) that was calibrated prior to each test with a 1-liter calibration syringe (ZAN 600, nSpire Health, CO, USA). Known gas concentrations of ambient and expired air (20.9/15.9 Vol% for O2, 0.03/5.0 Vol% for CO2, N2 in equilibrium) were used to calibrate the gas analyzers.

Parallel to exercise testing, heart rate (HR) was recorded with a beat-to-beat monitoring system (T4, Suunto, Vantaa, FIN) to determine exercise training intensity. The intensity was set at a HR equaling the pre-training work rate at ANT and RCP.

Based on the incremental test protocol, ventilatory thresholds were determined by visual inspection and stepwise linear regression utilizing a tri-segmental model ([10](#_ENREF_10),[47](#_ENREF_47)). POE was determined by the disproportional increase in VE vs. VO2 ([20](#_ENREF_20)). ANT was assessed by the time curve of the PETO2 and PETCO2 as well as by the time course of the ventilation equivalent for oxygen and carbon dioxide (VE/VO2, VE/VCO2) as described by Scheuermann and Kowalchuk ([45](#_ENREF_45)). RCP was determined by the disproportional increase in VE vs. VCO2 production according to Wassermann et al. ([56](#_ENREF_56)). Test-retest and the observer reliability of the determination of VTs accounted for POEr = 0.94 and r = 0.97, for ANTr = 0.89 and r = 0.99, and for RCPr = 0.95 and r = 0.97, respectively, utilizing a 10 W·min-1 cycling increment ([54](#_ENREF_54)).

**Exercise Training**

To improve aerobic capacity, a progressive stationary cycle training program was selected ([14](#_ENREF_14),[19](#_ENREF_19)). The 10-wk exercise program consisted of 3 sessions·wk-1 fully supervised, each including 5 min of warm-up and cool-down, respectively, and 35 min for the 1st 3 wks followed by 50 min for remainder of the core workout. The sessions were completed at least 48 hrs apart. The exercise prescription is depicted in detail in Table 1, where three zones of exercise intensity were prescribed via the HR equaling a workload at 80 to 100% of ANT, 90 to 100% of RCP, and 100 to 120% of RCP, respectively. Heart rate was recorded every session to assess differences between planned and completed exercise dosage. Subject data were included when an exercise training compliance of ≥80% was achieved.

**Table 1. Distribution of Exercise Intensity Zones (min) Over 10 wks.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Week** | **Session 1 (min)** | **Session 2 (min)** | **Session 3 (min)** |
|  |  |  |  |
| **1** | 45a | 60a | 45a |
| **2** | 60a | 45a | 60a |
| **3** | 60a | 60a | 60a |
| **4** | 60 (2 x 10 +40)b | 60a | 60 (2 x 10 +40)b |
| **5** | 60 (3 x 10 +30)b | 60a | 60 (2 x 15 +30)b |
| **6** | 60 (2 x 10 +40)b | 60a | 60 (4 x 5 +40)c |
| **7** | 60a | 60a | 60 |
| **8** | 60 (3 x 10 +40)b | 60a | 60 (4 x 5 +40)c |
| **9** | 60 (3 x 10 +40)b | 60a | 60 (6 x 5 +30)c |
| **10** | 60 (5 x 5 +35)c | 60 (2 x 20 +20)b | 60 (6 x 5 +30)c |
|  |  |  |  |

**Exercise intensity zones as:** aHR at 80 to 100% of ANT, bHR at 90 to 100% of RCP, and cHR at 100 to 120% of RCP.

**Statistics**

Normality was tested with Shapiro-Wilk statistics as suggested for small sample sizes ([39](#_ENREF_39)). Chi-squared test was utilized to test the allele frequencies for Hardy-Weinberg equilibrium. The one way analysis of variance (ANOVA) was conducted to determine mean differences between genotypes of primary outcomes at baseline (Table 2 and 3). Interaction of genotype and exercise training was tested with analyses of variance (ANOVA) for repeated measures, and training effects within groups were tested with paired sample *t* test and reported as absolute differences of post minus pre measures in Table 4. Because genotype group were not different from each other in all outcome measures at baseline and because of the small range in age of the investigated male sample no covariates were used to adjust the measures. Significance level was set at P≤0.05. Statistical procedures were carried out using the Statistical Package for Social Sciences (SPSS 17.0, Chicago, IL, USA).

**RESULTS**

All allele frequencies were in Hardy-Weinberg equilibrium as tested by Chi-squared test. The overall genotyping success rate was 96.6% for rs8192678 (Ser482 encoding allele). Rescreening of 5% of the 440 subjects resulted in 100% identical results. All data were normally distributed for each group (GT1, GT2, GT3) at both time points (0, 10 wks). Accordingly, repeated ANOVA was performed and the F-test results were used because of equally distributed variance for all variables.

**Baseline Outcomes: Anthropometric, Blood and Exercise Performance Data**

As depicted in Table 2, male subjects were middle-aged with 58 ± 6 yrs, overweight according to a BMI ≥25 kg·m-2 and characterized by an elevated cardiovascular risk according to a waist circumference of >94 cm with a normal body fat composition ([26](#_ENREF_26),[59](#_ENREF_59)). Based on the IDF definition (i.e., waist circumference, blood pressure, TG-concentration, HDL-C, and fasting plasma glucose), about every third participant suffered from the MetS with no effect of the investigated genotype on the occurrence rate of the MetS (see Table 2).

The performance level at baseline, assessed as VO2 or work rate (P) at ventilatory thresholds and at maximum load, did not differ significantly between genotypes as recorded in Table 3. The subjects are characterized by an average cardiorespiratory fitness of 35.3 ± 5.4 mL·kg-1·min-1 regarding their age strata ([32](#_ENREF_32)).

**Table 2. Baseline Characteristics of Subjects According to Genotype.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Groups** | **Total** | | **GT1** | | **GT2** | | **GT3** | |  |
| **SNP-*PPARGC1A*** | **G/A, G/A, A/A** | | **G/G (Gly/Gly)** | | **A/A (Ser/Ser)** | | **G/A (Gly/Ser)** | | **P** |
|  |  | |  | |  | |  | |  |
| **Sample size** (n) | **24** | | **8** | | **8** | | **8** | |  |
| **Age** (yrs) | 58.3 | ± 5.7 | 58.5 | ± 6.2 | 57.6 | ± 5.4 | 58.8 | ± 6.2 | ns |
| **BM** (kg) | 87.2 | ± 7.6 | 88.2 | ± 4.6 | 88.2 | ± 9.1 | 85.3 | ± 8.8 | ns |
| **BMI** (kg·m-2) | 27.6 | ± 2.7 | 27.2 | ± 1.9 | 28.2 | ± 2.9 | 27.3 | ± 3.4 | ns |
| **LBM** (kg) | 37.7 | ± 2.2 | 38.2 | ± 1.3 | 37.4 | ± 2.2 | 37.6 | ± 3.0 | ns |
| **BF** (kg) | 16.6 | ± 5.0 | 16.3 | ± 2.8 | 18.4 | ± 6.1 | 15.1 | ± 5.6 | ns |
| **Waist** (cm)° | 101.3 | ± 7.3 | 101.4 | ± 4.7 | 104.1 | ± 8.5 | 98.5 | ± 8.1 | ns |
| **SBP** (mmHg)° | 136 | ± 15 | 131 | ± 8 | 137 | ± 16 | 139 | ± 20 | ns |
| **DBP** (mmHg)° | 85 | ± 8 | 83 | ± 5 | 86 | ± 11 | 85 | ± 8 | ns |
| **TG** (mg.dL-1)° | 99.8 | ± 52 | 97.3 | ± 61.5 | 95.6 | ± 43.5 | 106.0 | ± 52.0 | ns |
| **HDL-C** (mg.dL-1)° | 58.3 | ± 15.1 | 54.0 | ± 11.5 | 64.9 | ± 14.7 | 56.8 | ± 18.4 | ns |
| **FPG** (mg.dL-1)° | 96.1 | ± 9.0 | 97.5 | ± 10.3 | 96.4 | ± 10.2 | 94.5 | ± 7.2 | ns |
| **MetS** (n within group) | 9/24 | (38%) | 3/8 | (38%) | 2/8 | (25%) | 4/8 | (50%) |  |
|  |  |  |  |  |  |  |  |  |  |

Values are means ± SD after one-way ANOVA; GT1 = common allele type in *PPARGC1A* (G/G), GT2 = homozygous for rare allele frequency in *PPARGC1A* (A/A), GT3 = heterozygous for rare allele frequency in *PPARGC1A* (G/A); BM = body mass, BMI = body mass index, LBM = lean body mass, BF = body fat, SBP = systolic blood pressure, DBP = diastolic blood pressure, TG = triacylglycerol, HDL-C = high density lipoprotein cholesterol, FPG = fasting plasma glucose, MetS = subjects with metabolic syndrome; °variables of MetS; P = significance level between the genotype groups; ns = not significant.

**Table 3. Submaximal and Maximal Performance Markers by Genotype at Baseline.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Groups** | **Total** | | **GT1** | | **GT2** | | **GT3** | |  |
| **SNP-*PPARGC1A*** | **G/A, G/A, A/A** | | **G/G (Gly/Gly)** | | **A/A (Ser/Ser)** | | **G/A (Gly/Ser)** | | **P** |
|  |  | |  | |  | |  | |  |
| **Sample size** (n) | **24** | | **8** | | **8** | | **8** | |  |
| **VO2-POE**(mL·kg-1·min-1) | 20.0 | ± 3.3 | 19.3 | ± 4.0 | 20.7 | ± 2.6 | 20.1 | ± 3.2 | ns |
| **VO2-ANT** (mL·kg-1·min-1) | 20.6 | ± 5.2 | 17.5 | ± 3.5 | 21.6 | ± 4.1 | 22.7 | ± 6.1 | ns |
| **VO2-RCP** (mL·kg-1·min-1) | 28.0 | ± 4.7 | 26.7 | ± 4.7 | 28.2 | ± 4.5 | 29.1 | ± 5.3 | ns |
| **VO2peak** (mL·kg-1·min-1) | 35.3 | ± 5.4 | 34.1 | ± 4.8 | 35.7 | ± 5.1 | 36.3 | ± 6.6 | ns |
| **PPOE** (W) | 109.1 | ± 17.0 | 105.0 | ± 20.7 | 117.1 | ± 15.0 | 106.3 | ± 14.1 | ns |
| **PANT** (W) | 119.6 | ± 30.3 | 105.0 | ± 29.3 | 127.5 | ± 23.8 | 126.3 | ± 35.0 | ns |
| **PRCP** (W) | 166.7 | ± 26.5 | 160.0 | ± 22.7 | 172.5 | ± 26.0 | 167.5 | ± 32.0 | ns |
| **Pmax** (W) | 217.5 | ± 31.1 | 208.8 | ± 24.7 | 223.8 | ± 37.0 | 220.0 | ± 32.5 | ns |
|  |  |  |  |  |  |  |  |  |  |

Values are means ± SD after one-way ANOVA; VO2 = minute volume of the relative oxygen uptake, P = absolute work rate; POE = point of optimal respiratory efficiency, ANT = anaerobic threshold, and RCP = respiratory compensation point; P = significance level between GT-groups; ns = not significant.

**Trainability of Aerobic Capacity within Genotype Groups**

The distribution of the exercise intensity zones of all completed sessions for the entire sample accounted for 80% at the heart rate equaling HR@80-100% of ANT, 13% at HR@90-100% of RCP, and 7% at HR@100-120% of RCP. The compliance for 30 sessions was high and accounted for 99% in GT1, 94% in GT2 and 100% in GT3.

Within the total sample supervised cycling resulted in a significant decrease in BMI (P≤0.001), in body fat (-1 kg; P≤0.01), in diastolic blood pressure (-4 mmHg; P≤0.01), and in fasting plasma glucose (P≤0.05; see Table 4). One subject in GT1 and two subjects in GT3 became normal regarding the MetS (as depicted in Table 4). In addition, aerobic capacity (i.e., VO2 and mechanical power at submaximal level) improved significantly in the entire group at POE (VT1, P≤0.05) and at RCP (VT2, P≤0.001) at post-testing. Furthermore, aerobic power as VO2peak or Pmax increased significantly (P≤0.001) after 10 wks of cycling.

Within groups, significant absolute changes were found in BMI in GT1 and to a smaller extent in GT3, slightly in waist circumference in GT1 and in diastolic blood pressure in GT2. Aerobic capacity as VO2 improved significantly in GT1 at ANT, RCP and maximum level compared to a smaller increase at RCP and maximum level in GT3. No improvement was found in the homozygous rare allele group GT2. Work rate as absolute change in Watt increased significantly at all three submaximal markers, compared to a significant increase of P at RCP in GT3, or no effect in GT2. Maximal work rate improved in all genotypes, with the largest increase of +33 W in GT1, followed by GT3 (+31 W) and by GT2 (+20 W).

Of interest is the finding of a significant interaction between genotype and exercise in the work rate at RCP (P≤0.05), which demonstrates a significant smaller response in males carrying the homozygous rare allele in *PPARGC1A* compared to a larger response in GT3 (heterozygous for the rare allele) and the highest change of +28 W at RCP in the wild type group (Table 4).

**Table 4. Exercise-Induced Trainability as Absolute Changes within 10 wks in Subject Characteristics, Clinical Data, Submaximal and Maximal Performance Markers Regarding Genotype.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total** | | **GT1** | | **GT2** | | **GT3** | |  |
| **SNP-PPARGC1A** |  | | **G/G** | | **A/A** | | **G/A** | | **P** |
|  |  | |  | |  | |  | |  |
| **N** | **24** | | **8** | | **8** | | **8** | |  |
| **BMI** (kg·m-2) | -0.4 | ± 0.5\*\*\* | -0.4 | ± 0.2\*\*\* | -0.5 | ± 0.7 | -0.3 | ± 0.4\* | ns |
| **LBM** (kg) | -0.3 | ± 1.3 | -0.3 | ± 1.4 | -0.4 | ± 1.7 | 0.0 | ± 0.9 | ns |
| **BF** (kg) | -0.9 | ± 1.4\*\* | -0.7 | ± 1.4 | -1.2 | ± 1.8 | -0.8 | ± 1.1 | ns |
| **Waist** (cm) | -1.8 | ± 4.6 | -1.8 | ± 1.5\* | -3.9 | ± 7.4 | 0.5 | ± 1.3 | ns |
| **SBP** (mmHg) | -6 | ± 13 | -6 | ± 10 | -7 | ± 15 | -4 | ± 16 | ns |
| **DBP** (mmHg) | -4 | ± 7\*\* | -3 | ± 7 | -6 | ± 6\* | -2 | ± 7 | ns |
| **TG** (mg·dL-1) | 19.7 | ± 64.4 | 16.8 | ± 44.2 | 40.6 | ± 86.2 | 4.4 | ± 63.1 | ns |
| **HDL-C** (mg·dL-1) | 1.0 | ± 9.6 | 3.3 | ± 5.4 | -3.4 | ± 11.7 | 2.8 | ± 10.7 | ns |
| **FPG** (mg·dL-1) | -3.4 | ± 6.6\* | -3.9 | ± 6.1 | -3.1 | ± 8.2 | -3.3 | ± 6.5 | ns |
| **MetS**  (n within group) | **6/24** | **(25%)** | **2/8** | **(25 %)** | **2/8** | **(25%)** | **2/8** | **(25%)** |  |
| **VO2-POE** (mL·kg-1·min-1) | 1.4 | ± 2.4\* | 2.2 | ± 2.9 | 0.7 | ± 1.7 | 0.9 | ± 2.3 | ns |
| **VO2-ANT** (mL·kg-1·min-1) | 1.6 | ± 4.6 | 3.7 | ± 3.4\* | 0.1 | ± 4.0 | 1.1 | ± 5.8 | ns |
| **VO2-RCP** (mL·kg-1·min-1) | 2.0 | ± 3.3\*\* | 3.8 | ± 4.4\* | 0.5 | ± 2.6 | 1.8 | ± 1.6\* | ns |
| **VO2peak** (mL·kg-1·min-1) | 2.9 | ± 3.1\*\*\* | 4.0 | ± 3.7\* | 2.7 | ± 3.5 | 2.1 | ± 2.1\* | ns |
| **PPOE** (W) | 13.5 | ± 22.9\*\* | 18.8 | ± 15.5\*\* | 2.9 | ± 24.3 | 17.5 | ± 27.1 | ns |
| **PANT** (W) | 10.4 | ± 26.3 | 21.3 | ± 13.6\*\* | -2.5 | ± 12.8 | 12.5 | ± 39.9 | ns |
| **PRCP** (W) | 17.5 | ± 20.7\*\*\* | 28.8 | ± 25.9\* | 3.8 | ± 16.9 | 20.0 | ± 9.3\*\*\* | .04 |
| **Pmax** (W) | 27.9 | ± 13.2\*\*\* | 32.5 | ± 13.9\*\*\* | 20.0 | ± 12.0\*\* | 31.3 | ± 11.3\*\*\* | ns |
|  |  |  |  |  |  |  |  |  |  |

Values are means ± SD after paired sample *t* test as absolute differences (post – pre), \*P≤0.05, *\*\**P≤0.01, and *\*\*\**P≤0.001 pre- vs. post-measures; P depicts the interaction of genotype and exercise training tested by ANOVA with repeated measures; ns, not significant; other abbreviations see notes of Table 1.

**Comparability of Ventilatory Thresholds**

At pre- and post-testing VO2 and work rate at RCP were significantly higher compared to the mean values at POE or AT. Although at baseline the work rate in Watt at POE was 11 W lower than at ANT, the difference was not significant, and this difference was not found at post-testing. In summary, the level of POE and ANT were nearly similar in untrained middle-aged male subjects (see Table 5).

Accordingly, VO2-POE and VO2-ANT were achieved at 57 and 58% of VO2peak compared to VO2-RCP, that was achieved at 79% of VO2peak at baseline. After 10 wks of cycling, aerobic capacity as VO2-POE was found at 56%, VO2-ANT at 58%, and VO2-RCP at 78% of VO2peak (38.3 ± 5.6 mL·kg-1·min-1), indicating the relative stability of aerobic capacity over 10 wks of cycle training.

**Table 5. Differences in VO2 and in Work Rate between Ventilatory Thresholds Before and After 10 wks Cycling.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **N = 24** | | **POE** | | **ANT** | | **RCP** | |  |
|  |  | **M** | **± SD** | **M** | **± SD** | **M** | **± SD** | **P** |
|  |  |  |  |  |  |  |  |  |
| **VO2-pre** | (mL·kg-1·min-1) | 20.0 | ± 3.7 | 20.6 | ± 5.1 | 28.0 | ± 4.7*a* | .0001 |
| **VO2-post** | (mL·kg-1·min-1) | 21.3 | ± 3.0 | 22.2 | ± 4.5 | 30.0 | ± 5.3*a* | .0001 |
| **P-pre** | (W) | 109.1 | ± 17.0 | 121.4 | ± 32.6 | 166.1 | ± 28.6*a* | .0001 |
| **P-post** | (W) | 122.6 | ± 24.2 | 128.6 | ± 27.2 | 186.8 | ± 31.5*a* | .0001 |
|  |  |  |  |  |  |  |  |  |

Values are means ± SD tested by ANOVA for repeated measures at pre- and post-testing adjusted for multiple comparison (Bonferroni); *a*RCP-level significant different from ANT and POE at P≤.0001; other abbreviations see notes of Table 1.

**DISCUSSION**

In this prospective study, we investigated the effect of the rs8192678 point mutation in the *PPARGC1A* gene on oxidative capacity of middle-aged untrained males after 10 wks of stationary supervised cycling. Such endurance type exercise is highly recommended in adults to improve their cardiorespiratory fitness and metabolic health ([19](#_ENREF_19),[46](#_ENREF_46)).

**Metabolic Syndrome**

Because of the small sample size we discuss the data on a descriptive level. After 10 wks of training, 3 of 9 males were no longer characterized by MetS. The finding that regular exercise is able to reduce the occurrence rate of MetS was reported widely over the last decade as reviewed by Roberts, Hevener, and Barnard ([42](#_ENREF_42)). Subjects with low expression of *PPARGC1A* showed a dysfunction in the regulation of inflammation and lipid oxidation, two components among many others associated with the development of the MetS ([36](#_ENREF_36),[42](#_ENREF_42)). However, the results of our small sample could not be proof of this observation since 2 to 3 subjects with MetS were found in each genotype group pre- and post-testing.

**Maximum Performance Level and Aerobic Power Were Not Affected by Genotypes**

Although maximum work rate increased sufficiently by 13% after exercise training, no significant effect of genotype could be detected because of the large variation in work rate and in VO2peak after 30 cycling sessions in formerly untrained men. This is in line with Stefan et al. (51), who detected a smaller increase of +2% after a 2-yr lifestyle intervention with no effect of SNP in *PPARGC1A* on aerobic power compared to our prospective study. On average, the entire sample improved aerobic power significantly by +8%, a low-to-moderate response that is often found after short-term exercise intervention ([27](#_ENREF_27),[41](#_ENREF_41)).

The measured exercise-induced variation in VO2peak is in accordance with 6 wks of cycling at 70% of VO2peak of young males 23 ± 5 yrs of age (range: -2% to 23%), but in contrast to 10 wks of cycling at 70 to 90% VO2peak (+31 ± 10%) in males aged 68 ± 7 yrs ([34](#_ENREF_34),[55](#_ENREF_55)). One reason for a higher response in older males could be the initial performance level, as they started with a 20% lower cardiorespiratory fitness and a lower Pmax of 180 W compared to a Pmax of 218 W achieved in the present study. In contrast to that argument are the results of the Heritage-Family Study, indicating that other factors than the initial fitness level explain the variation in exercise-induced VO2 max after 20 wks of cycling ([46](#_ENREF_46)).

Another reason for the smaller response in VO2peak could be explained by the exercise intensity. In the present study, the volume of high-intensity (HIT) bouts, that led to heavy muscle strain as reported by our male subjects but was recommended for untrained subjects ([17](#_ENREF_17)), accounted for 7% of total sessions. However, the distribution of intensity zones in our study of 80-13-7% (HR@80-100%ANT - HR@90-100%RCP - HR@100-120%RCP) was very close to Esteve-Leano et al. (14) of 80-10-10%. They showed that cycling below the RCP resulted in a significantly higher performance level measured as a longer lasting time trial test compared to athletes completing a greater anaerobic portion. Consequently, we are not able to draw the conclusion that exercise intensity was too low for a sufficient improvement in aerobic power.

Moreover, we propose that the short exercise intervention of 10 wks and the smaller number of 30 sessions compared to 50 sessions in the Esteve-Leano et al. (14) study may have accounted for a delay in adaptation at the cellular level. This would result in a smaller effect at maximal performance level and a broad variation in trainability from low to high responder ([16](#_ENREF_16),[41](#_ENREF_41),[55](#_ENREF_55)). Accordingly, we suggest that the short exercise intervention determines the large variation in training response at maximum level, where the structural adaptation on the cardiovascular and/or cellular level in some participants is ongoing and in others is already finished ([4](#_ENREF_4)). Another reason could be that the rs8192678 SNP, who was not upon the 21 SNPs found to affect the trainability of VO2max, is not associated to impact the trainability of aerobic power ([5](#_ENREF_5)). As suggested recently by Vollaard et al. (55) and by others, a more sensitive measure of trainability after a short-term exercise intervention may be submaximal markers ([30](#_ENREF_30),[31](#_ENREF_31),[37](#_ENREF_37),[52](#_ENREF_52)).

**Genotype and Submaximal Markers at Baseline**

Genotype did not significantly affect the occurrence of VTs at baseline as reported by Stefan and colleagues ([51](#_ENREF_51)). The finding that at baseline the workload at POE was lower than at ANT and at RCP was found by Wisen and Wolhfart (60). However, the differentiation between POE and ANT was not significant at baseline and diminished after 30 sessions of cycling by using the same exercise testing protocol. Moreover, the result is not in line with further observations in our laboratory that especially trained compared to untrained subjects exhibited a lower VO2 and work rate at POE vs. ANT, as the differentiation diminished after exercise training. To date it seems that POE and ANT are markers for the first VT and RCP identifies the second VT as suggested by Westhoff et al. ([58](#_ENREF_58)).

**Trainability**

***Genotype and Exercise Induced Changes of Aerobic Capacity:*** In agreement with the retrospective study of Stefan and colleagues (51), we found a reduced effect in VO2 and work rate at submaximal performance level. In addition to this, there is an indication that the effect is more prominent in subjects homozygous for the rare frequency gene variant of *PPARGC1A* (A/A) than in heterozygous males or in males with the common frequency allele.

Evidence for an impact of the *PPARGC1A* gene variant (rs8192678) on aerobic performance was also found in endurance athletes who were characterized by a lower rare allele frequency compared to untrained European males ([1](#_ENREF_1),[15](#_ENREF_15),[28](#_ENREF_28),[29](#_ENREF_29)). Moreover, a smaller proportion of the investigated rare allele in *PPARGC1A* was associated with a significantly higher cardiorespiratory fitness (VO2peak) and percentage of slow-twitch fibers compared to untrained, unrelated healthy men and women ([1](#_ENREF_1)). Additionally, it has been shown in a Polish cohort that the frequency of the rare allele in *PPARGC1A* was significantly less evident in endurance, strength-endurance and sprint-strength trained athletes compared to untrained controls (5.6% vs. 13.2%, P<0.0001), which was analyzed with the same genotyping method (29) as was used in the present study. Furthermore, a significant smaller proportion of the rare allele frequency of rs8192678 (*PPARGC1A* - G/A) was found in soccer players compared to healthy controls, indicating that regular moderate-to-vigorous physical activity is associated with the *PPARGC1A* allele ([18](#_ENREF_18)). In line with this finding, denHoed et al. (12) reported recently that the SNP rs8192678 is negatively associated to the amount of habitual physical activity.

**CONCLUSION**

All together the data indicate that the rs8192678 SNP is associated to the exertion of chronic exercise. However, short-term exercise intervention can diminish the impact of SNP in heterozygous males, probably by affecting function-specific domains to the *PPARGC1A* gene and by altering a subset of the multiple processes that PGC1 regulates on mitochondrial level as suggested by Lai et al. (25) in diabetic subjects.

Despite a small sample size, the present study provides clear evidence that untrained males carrying the rare allele in the *PPARGC1A* gene (rs8192678) respond less to a supervised stationary cycling training based on VO2 and work rate at RCP compared to subjects carrying the common allele frequency. This interaction is largest in the homozygous condition. The relevance of these results is further underpinned by the fact that the subjects were prospectively selected by defined genotypes containing the above SNP and by a supervised exercise intervention. Accordingly, we recommend monitoring of submaximal markers rather than changes in peak oxygen uptake when investigating the effects of an exercise intervention in combination with the *PPARGC1A* gene variants.

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SRD is the principle investigator and wrote the main part of the article. She is responsible for study design, subject recruitment, exercise intervention, data analysis, funding, and coordination of the research groups. LK and IK genotyped the DNA samples from the SAPHIR-cohort and wrote the parts related to genotyping. RF, PS, WS, HF, TF, EM and BK were involved into the study design, testing and in careful reading of the paper. BP is the senior researcher, who had the idea for the study, was involved into the study design and in careful reading of the paper.

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