TRABAJO FIN DE MÁSTER

Máster en Actividad Física y Salud

Relación entre la oxidación de grasas y el consumo de oxígeno en la enfermedad de McArdle

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1. Introducción.

1.1 ¿Por qué se ha elegido este tema?

Se ha decidido elegir este tema porque las primeras clases del máster fueron con Dr. Alfredo Santalla, donde nos habló sobre fisiología del ejercicio, así como de su relación con la enfermedad de McArdle. Nunca había oído hablar de esta patología y me pareció muy interesante, ya que me ayudó a entender muchos aspectos de la fisiología general. Además, tuvimos la oportunidad de hacer una prueba de esfuerzo con un paciente y ver el tipo de entrenamiento que era más beneficioso para él.

Tener la oportunidad de entrenar con este paciente y conocer cómo cambia su calidad de vida, despertó mi interés sobre esta patología y sobre cómo poder ayudar a estos pacientes para que se sientan mejor en su día a día.

1.2 ¿Qué preguntas / hipótesis pretende contester la investigación?

A la hora de realizar esta investigación, la principal hipótesis que se pretende contrastar es si al aumentar la capacidad de oxidar grasas a una intensidad submáxima y constante, y con una carga determinada para provocar el segundo aliento, mejorará la tolerancia máxima al ejercicio (W pico) y la aptitud física (VO2 pico).

1.3 ¿Por qué se decidió seguir la metodología utilizada?

Se ha elegido esta metodología porque se trata de una muestra menor de 40, por lo que utilizamos Kolmogorov – Smitnov, y, posteriormente, el coeficiente de correlación de Pearson para evaluar la relación entre los parámetros de la aptitud aeróbica y las variables relacionadas con el fenómeno del segundo aliento (W al 60% de la FC máxima).

2 Principales problemas surgidos para llevar a cabo el estudio.

Al no estar presente desde el inicio del estudio, tanto el reclutamiento como las pruebas de esfuerzo, las han llevado a cabo los investigadores implicados y no se han encontrado con ningún contratiempo y a la hora de realizar el análisis de datos tampoco surgió ningún problema.

3 Características de la revista a la que se pretende enviar.

3.1 Motivos por los que se ha elegido la revista.

Se ha escogido esta revista porque tiene un gran prestigio a nivel mundial y, como se puede apreciar en las características que se muestran a continuación, pertenece al Q1 y está entre las 10 mejores revistas en Ciencias del Deporte. Otro de los motivos por los que se ha elegido la revista Medicine & Science in Sports & Exercise es porque ya se han publicado estudios previos relacionados con la enfermedad de McArdle como el de Munguia-Izquierdo et al. (2014), en dicha revista y considero que es un factor a tener muy en cuenta ya que podría significar que los lectores de esta revista están interesados en este tema.

3.2 Características de la revista.

En cuanto a las características de la revista que se ha elegido para enviar el artículo que se presenta en el próximo apartado, son las siguientes:

Tabla 1. Datos de la revista escogida para enviar el artículo.

Características de la revista	
Nombre de la revista	Medicine & Science in Sports & Exercise.
Editor principal	Andrew M. Jones. PhD
Categoría JCR a la que pertenece	Sport Sciences.
Cuartil 2021	Q1
Factor de impacto con autocitas	6.289
Factor de impacto sin autocitas	6.048
Ranking	9/87 en Ciencias del Deporte.
Citas totales	46.557
Editorial	Science Citation Index Expanded (SCIE).
ISSN de la revista	0195-9131
ISSN Online	1530-0315
País de publicación	Estados Unidos.
Periodicidad de publicación	12 artículos al año.
Página web de la revista	https://journals.lww.com/acsm-msse/pages/default.aspx

Nota: Características de la revista. **Fuente:** Elaboración propia.

4 Informe de autorización del comité ético.

El estudio sigue las guías éticas de la Declaración de Helsinki, y fue aprobada por el Comité Ético del Hospital 12 de Octubre, Madrid, España (número de aprobación 16/081). Además, se informó a todos los participantes acerca de los procedimientos del estudio y firmaron un consentimiento informado como el que se adjunta en el apartado de ANEXOS.

5 Artículo tal y como se enviará a la revista.

Relationship between submaximal Fat Oxidation and Peak Oxygen Uptake in McArdle Disease.

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ABSTRACT

Introduction: McArdle disease, is an autosomal recessive disease associated with the lack of energy production from the glycogen and exercise intolerance. This study aimed to study the relationship between fat oxidation capacity at submaximal constant intensity with the load needed to provoke the 2nd wind, maximal exercise tolerance (Wpeak) and fitness (VO_2peak).

Methods: Twenty – eight patients performed a two phases test; 1st phase: a 15-minute constant-load equivalent to 60% of maximal heart rate (HR), and, immediately after, a 2nd phase: incremental ramp test until exhaustion. Submaximal fat oxidation was measured in constant load, while all gas exchange parameters were recorded during incremental exercise.

Results: Strong correlation between the load at constant test and VO_2peak was found. There were also strong correlations between submaximal fat oxidation and the constant load at 60%HRmax, VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$) and Wpeak, while moderate correlation between submaximal fat oxidation and VO_2peak relativized to legs muscle mass ($mL \cdot min^{-1} \cdot kg^{-1}$) was found.

Conclusion: The present study corroborate the strong correlation between the load at 60%HRmax and VO_2peak, previously described, and showed that submaximal fat oxidation was strongly correlated with the constant load at 60%HRmax, VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$), and VO_2peak relativized to legs muscle mass ($mL \cdot min^{-1} \cdot kg^{-1}$).

Keywords: MYOPHOSPHORYLASE, EXERCISE IS MEDICINE, GLYCOGENOSIS TYPE 5, GLYCOGEN STORE DISEASE.

INTRODUCTION

Type V Glycogen storage disease (GSD-V) (Orpha: 368), McArdle disease, is an autosomal recessive disease (prevalence 1:140.000 **(1)**)caused by deficiency of the muscle enzyme myophosphorylase (one of the three isoforms of phosphorylase), due to mutation of the two alleles of the PYGM gene, that encodes it **(2)**. This, provokes the inability to degrade muscle glycogen to glucose 1-6 di-phosphate for energy from glycogen stores **(3)**.

Due to this lack of energy production from the glycogen, McArdle patients muscle cells suffer an impairment in its metabolic processes (i.e. Actine-myosin contraction, calcium regulation in the sarcoplasmic reticulum, sodium-potassium pump function, etc.) **(2)** that provokes a complex physiopathology, characterized exercise intolerance, muscle weakness, acute muscle crisis / contractures (specially in dynamic and isometric exercises), pain, rhabdomyolysis (muscle damage), myoglobinuria (dark urines), and hyper-CK-emia (most of them with a rest values CK above 1000 U/L, even without pain or contractures) **(2,3)**. Due this, a high percentage of McArdle patients are sedentary, and express more severe symptomatology and a lower peak oxygen uptake (VO_2peak) **(1,4)**, and less bone mass **(5)**, than those who maintain an active pattern of life.

One almost pathognomonic characteristic that clearly shows that metabolic deficiency provoke the exercise intolerance of patients with GSD-V is their response to constant load exercise, which known as "*second wind"* (6) . This consists of a rapid increase in the Rating of Perceived Exertion (RPE) and the muscle Rating of Perceived Pain (RPP), together with a hyperkinetic response of the Heart Rate (HR) in the first minutes of moderate exercise at constant load (i.e.

walking or pedaling at low load), which disappears after 6-10 minutes of exercise (4). This is mainly due to the increased flow of fatty acids and blood glucose into the muscle, facilitated by the vasodilator response during exercise, which increases their oxidation (7,8). In fact, it has been reported that it is possible to reduce the magnitude of the *"second wind"* by increasing blood glucose with pre-exercise isotonic ingestion (8). McArdle's patients suffer this phenomenon multiple times throughout the day (i.e., every time they walk), which, together with the pathophysiological characteristics described before, severely limits their quality of life (3).

Trying to reduce McArdle patients' symptomatology, and increase Quality of Life (QoL) a few exercise interventions has been done (9–14). All of these, have shown positive effects on VO2peak, severity of symptomatology, strength and exercise tolerance (3). Thus, it has been recently described that those McArdle patients who followed an active pattern of live, i.e following the WHO exercise recommendations (Aerobic exercise: at least 150 min/week of aerobic exercise in 5 days/week, and Strength Exercise (15). At least 2 non-consecutive days/week) show not only higher VO_2peak, exercise capacity (i.e W_{peak}) in incremental test, but also a higher load (W) needed to provoke the 2^{nd} wind in a constant exercise (9). This study shows an increase of oxidative capacity of the muscle cells (estimated as VO_2peak values, relativized to lower limbs muscle mass), that can be partially responsible for these maximal intensity adaptations. This maximal oxidative capacity has been shown to be lipid / fatty acid oxidative capacity, by indirect calorimetry in incremental step test (16). In this study, Rodríguez-López et al. tested 9 physically active / trained McArdle patients and showed significatively higher FatMax and fat oxidation rate (MFO) than healthy controls. (94% VO2peak and 0.53 g/min *vs* 41% VO_2peak and 0.33 g/min, respectively) (16). Since subjects

were in fasting conditions, which is a risky condition to do high intensity exercise for McArdle disease (3), authors decided to include only trained patients with experience in maximal lab tests. So, this study didn't include sedentary / untrained subjects.

It other way, in a large and heterogenic sample in terms of fitness (VO_2peak), a recent study have shown a transversal relationship between VO_2peak and the load (W) needed to provoke the 2nd wind in a constant exercise (normally tested at a 60% of maximal heart rate) (4). This relationship can be translated as that patients with higher VO_2peak would suffer less occurrence and magnitude of 2nd wind in the daily live activities (as many of them are in a lower intensity / load that the equivalent to a 60%HRmax). Despite patients were in fasting conditions, fat oxidation rate during constant tests was not measured.

Despite all this, together with the fact that clinical guidelines highlight the importance of training adaptations to improve VO_2peak and reduce the 2nd wind in McArdle patients (3), we don't know the existence of a study that focuses on the influence of fat oxidation capacity, measured a constant intensity on severity of 2nd wind and other maximal parameters. This could partially explain the VO_2peak-W2nd wind relationship previously described (4). The aim of this work was to study the possible relationship between fat oxidation capacity at submaximal constant intensity with the load needed to provoke the 2nd wind, maximal exercise tolerance (Wpeak) and fitness (VO_2peak).

METHODS

Participants

28 participants (14 male and 14 female) were evaluated in the Exercise physiology laboratory of the Universidad Europea de Madrid (UEM). The study adhered the ethics guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Hospital 12 de Octubre, Madrid, Spain (approval number 16/081). All participants were informed about the study procedures and signed a written informed consent.

Following previous methodology (4), inclusion criteria were: 1) diagnosis of McArdle Disease, as ascertained by identification of a documented pathogenic mutation in both alleles of the gene (PYGM) encoding phosphorylase, 2) being free o major cardiorespiratory disease o severe condition contraindicating exercise, 3) reporting the 2nd wind, and 4) having previous exercise testing experience in our laboratory.

Outcomes assessment

Body composition. Total and regional body composition was assessed by dual energy x-ray absorptiometry (DXA; Hologic Serie Discovery QDR, Software Physician's Viewer, APEX SystemSoftware Version 3.1.2. Bedford, MA, USA) **(10)**. Body mass composition was calculated from whole-body scans, which were submitted to a regional analysis to determine the composition of the arm, leg and trunk regions. Following previous methodology **(10)** the arm region encompassed the hand, forearm and arm, and was separated from the trunk by an inclined line that went across the scapula-humeral joint, in such way that the humeral head was positioned in the arm region. The leg region included the foot, the lower leg and the upper leg and was separated from the trunk by an inclined line crossing just below the pelvis, which crossed the neck of the femur. The trunk region included the entire body except the arms, legs and head sections. The head region was composed of all skeletal parts of the skull and cervical vertebra above a horizontal line crossing just below the jawbone. With this analysis, regional

body fat and lean mass can be evaluated with a coefficient of variation below 5%. This methodology has been previously used by our research group in McArdle patients **(17,18)**.

Aerobic fitness. The tests were done in an electrically braked cycle-ergometer (800S, Ergoline; Bitz, Germany) and pedal cadence was kept at 60-80 rpm. Participants first performed a 15-minute constant-load moderate-intensity test to induce the second wind, as recently described **(4)**. Workload was progressively increased until participants reached 60% of their estimated maximum HR (220 *minus* age in years) in the first three minutes of the test, and this workload was maintained for a total of 15 minutes. The same load was applied in the following condition/s. Immediately after the constant test, participants performed a ramp test until exhaustion. This test started with the workload applied in the constant test, which was subsequently increased by 5 watts every 30 seconds until volitional exhaustion or when one of the following criteria was met: contracture, participant unable to keep a pedal cadence ≥ 60 rpm, or RPE or RPP >9 **(16)**.

Gas exchange data were recorded 'breath by breath' during exercise with a metabolic cart (CPX Ultima, Medical Graphics Corporation, St Paul, NM). At the end of the constant-load test (average of the last minute), substrate (fat and CHO) oxidation was estimated with the equations proposed for 50-70%VO2max intensity by Jeukendrup (19) Fat oxidation = $(1.695 \cdot VO_2) - (1.701 \cdot VCO_2)$, and Carbohydrate oxidation = $(4.585 \cdot VCO_2) - (3.226 \cdot VO_2)$.

In the incremental phase of the test, ventilatory threshold (VT) was visually identified by two independent investigators (or by a third one in case of disagreement) as the workload eliciting an increase in the 30-s average value of the ventilatory equivalent for oxygen ($VE \cdot VO_2^{-1}$), with no concomitant increase in the ventilatory equivalent for carbon dioxide ($VE \cdot VCO_2^{-1}$) **(13)**.

The VO_{2peak} was determined as the highest VO_2 value (20-second average) recorded during the ramp tests. HR was continuously monitored using a 12-lead electrocardiogram (CPX Ultima, Medical Graphics Corporation, St Paul, NM, USA). To measure a possible increase in capacity to extract oxygen in recruited muscles, we calculate VO_2peak relative to the lower-body muscle mass (VO_2R) in $mLO_2 \cdot min^{-1} \cdot kg^{-1}$, following previous methodology used in McArdle disease **(9)**.

Blood lactate (Lactate Plus, Nova Biomedical, Waltham, MA) and glucose (FreeStyle Freedom Lite, Abbott, Chicago, IL) were measured in rest (pre-test), in the constant test once passed the 2nd wind (min 14) and at maximal intensity / extenuation (immediately post-test)

Statistics analysis.

Data are expressed in mean ± standard deviation. The distribution of data was studied with the Kolmogorov-Smirnov test. Pearson correlation analysis were used to assess the relationship between aerobic fitness parameters and variable related to 2nd wind phenomenon (W at 60% HRmax). The level of significance was set at 0.05 and data analysis was performed using SPSS statistical software package (online version). Only moderate ($0.4 < r < 0.6$) and strong correlations ($r > 0.6$) were taken account to the analysis.

RESULTS

Subjects' data are show in **table 1**.

Average physiological responses to constant and incremental phase of the test are shown in **table 2**.

Significatively correlations were found between VO_2peak and Load at constant test **(figure 1)**. Moreover, significatively correlations were found between fat oxidation rate ($g \cdot min^{-1}$) at constant work test and 1) load at constant work, 2) VO_2peak, and 3) VO_2peak relativized to lower limb muscle mass **(figure 2)**.

No more strong correlations were found between analyzed variables.

DISCUSSION.

The main findings of the present study were that 1) there was a strong correlation between the load at 60%HRmax and VO_2peak, 2) fat oxidation at 60%HRmax was strongly correlated with the constant load at 60%HRmax, VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$), and VO_2peak relativized to legs muscle mass ($mL \cdot min^{-1} \cdot kg^{-1}$).

Results of the present study showed a strong correlation ($r > 0.7$) between the load at 60%HRmax (in W) and VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$). Our data are in line with the previous reported by Salazar-Martinez et al. (4), in which the same strong correlation was found. Despite this correlation is not a novel finding in our study, our data allow to confirm the previous association between submaximal and maximal values. Salazar-Martinez et al. argued that this relationship as those McArdle patients with higher fitness (VO_2peak) would suffer less 2nd wind (in frequency and magnitude) in their daily life activities, because most of them would be below 60%HRmax (vs lower fit McArdle patients). Given the 2nd wind is present the most of patients, several time, and it clearly impacts on their QoL (1,3), we think important to confirm this relationship, but also it would be even more important to know the reasons that could explain it.

There was a strong correlation between submaximal oxidation rate at constant load and the load (W) needed to achieve 60%HRmax (and so, to suffer the 2nd wind). As there were no significant differences in lactate o glucose between min 0 and min 14 (pre-exercise and end of constant phase of the test, respectively), and since there was no correlation between (neither difference min 0- min 14), theses data clearly show that the increase in submaximal fat oxidation is the main adaptation responsible to reduce 2nd wind occurrence / magnitude in McArdle people, which is one of the main findings of this study. This is line with both, laboratory and clinical data described in the literature. By one hand, McArdle cohort studies have shown a low respiratory exchange ratio (RER) at submaximal and maximal intensities (1,4,9,16) that express not only a high percentage of fat oxidation during it, but also a higher MFO (vs healthy controls) (16). In the same way this RER has ben shown to decrease as adaptation to training (data of our laboratory). More over some of them has longitudinally showed increases in fitness (VO2peak) accompanied with decreases in severity class (9,10,13,14). By the other, transversal studies has shown that that those patient more active, show higher levels of fitness (VO2peak) and lower severity class (9,20). So, it seems that it would be important to understand physiological adaptations that aloud to improve VO_2peak, and then, to decrease symptomatology in those patients.

In this line, other important finding of the present study was a correlation between submaximal fat oxidation with VO_2peak (mL·min-1·min-1). It is known that McArdle Patient response to incremental step exercise is characterized by an increase in fat oxidation (16), where carbohydrates oxidation almost provide significative percentage of energy (21), as this disease Is characterized by a block in muscle glycogenolysis (2,3). Consequently of this glycogenolysis

block, it has been described a flat response (no increase) of lactate and H+ in incremental tests (22). This lack of blood lactic acidosis provokes an attenuated ventilatory response (22), and also a lack of lipid oxidation impairment (16), as is the drop in muscle pH the stimulus that inhibit the fatty acid metabolism (23). That's why fat oxidation increases lineally with the load and FatMax is very close to VO_2peak in McArdle patients (16). For all this, and together with the submaximal fat oxidation – VO_2 peak strong correlation founded, this data suggests clearly that the fat oxidation capacity improvement (as adaptation to exercise) mainly explains the submaximal load – VO_2peak correlation founded by Salazar-Martinez et al (4) and corroborate by us in the present study. This, is another find of this study and, in our opinion, could be interpreted as the reduction of symptomatology perceived by McArdle patients as adaptation to aerobic training (9,13,14) is mainly due to an increase in fat oxidation capacity.

Finally, a moderate ($r = 0.549$) correlation between submaximal fat oxidation and VO_2 relativized to legs muscle mass was found. This corroborate the correlations previously described and suggests that the increase in submaximal oxidation is also reflected in a higher oxidative capacity of recruited motor unit during exercise, and the fat oxidation as responsible of it, since the VO_2peak relative to legs muscle mass has been shown to increase an adaptation to training (9). However, submaximal fat oxidation correlation changed from strong to moderate (with VO_2peak and VO_2peak relative to legs muscle mass, respectively). We don't have a possible explanation of this, but we must highlight that correlation coefficient were very similar anyway (0.63 and 0.55, respectively).

In summary the results of the present study corroborate the strong correlation between the load at 60%HRmax and VO_2peak, previously described, and showed that submaximal fat oxidation

was strongly correlated with the constant load at 60%HRmax, VO_2peak ($mL \cdot kg^{-1} \cdot min^{-1}$), and VO_2peak relativized to legs muscle mass ($mL \cdot min^{-1} \cdot kg^{-1}$).

Conflicts of interest

The authors declare no conflicts of interest. The results of the present study do not constitute endorsement by ACSM, and are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Table 1. Anthropometric and descriptive data.

Variables	McArdle (n=28)
Age (years)	37.53 ± 2
Body mass (kg)	67.50 ± 11
Height (cm)	169.07 ± 6.3
BMI, ($kg \cdot m^{-2}$)	23.63 ± 3.9
Body fat mass (%)	30.30 ± 8.4

Table 2 Physiological responses to the ramp test in all participants (n =28).

Variable	Ramp test until exhaustion	
	Ventilatory threshold	Peak values
VO_2 ($mL \cdot min^{-1}$)	1040.46 ± 335.7	1475.10 ± 500.4
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	15.47 ± 4.8	30.24 ± 46.03
VO2/Leg muscle mass ($mL \cdot min^{-1} \cdot kg^{-1}$)	70.3 ± 18.5	87.62 ± 23
Power output (watts)	52.5 ± 17.6	85.46 ± 25.5
Power output/Leg muscle mass ($watts \cdot kg^{-1}$)	3.9 ± 1.2	5.6 ± 1.4
HR (bbm)	120.07 ± 18	160.55 ± 26.3
VE ($l \cdot min^{-1}$)	23.89 ± 5.6	41.29 ± 12.4
RER	0.82 ± 0.04	0.88 ± 0.9

Abbreviations: HR, heart rate; RER, respiratory exchange ratio; VE, pulmonary ventilation; and VO_2, oxygen uptake.

Figure 1. Correlation between load at constant test (W) and VO_2 Peak ($mL \cdot kg^{-1} \cdot min^{-1}$).