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Trabajo Original

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# Oxygen pulse as a protective factor of insulin resistance in sedentary women with overweight or obesity

## *Pulso de oxígeno como factor protector de resistencia a la insulina en mujeres sedentarias con sobrepeso u obesidad*

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## Abstract

**Background:** obesity is associated with insulin resistance (IR). Through exercise, insulin resistant obese patients can effectively improve their cardiorespiratory fitness (CRF). The effect of exercise on patients CRF can be determined by oxygen pulse ($PO_2$) analysis. Despite its usefulness, there is limited literature on $PO_2$ analysis in patients with obesity and insulin resistance.

**Objective:** the goal of the present study is to evaluate the relation between $PO_2$ and IR in sedentary obese women.

**Methods:** fifty-five women were submitted to a maximal exercise test for evaluation of maximal oxygen consumption and $PO_2$. The subjects with a homeostatic model assessment of IR index greater or equal to 2.5 were considered as insulin-resistant (IR). Participants were divided into two groups, IR group (n = 35) and non-IR group (n = 20).

**Results:** the IR group had lower values of $PO_2$ relative to body weight (11.0 ± 1.7 *versus* 12.6 ± 1.4 ml·kg·beats$^{-1}$, p = 0.001) and relative to lean mass (21.7 ± 2.9 *versus* 23.2 ± 2.8 ml·kg·beats$^{-1}$, p = 0.038) than non-IR group. No statistical differences were found in maximal oxygen consumption between the groups (non-IR = 1.53 ± 0.27 l·min$^{-1}$, IR = 1.51 ± 0.28 l·min$^{-1}$; p = 0.386). $PO_2$ relative to body weight and HOMA-IR was inversely correlated (p < 0.001; r = -0.465). Logistic regression analysis showed an association between $PO_2$ relative to weight (p = 0.001, OR = 0.47) and fat free mass (p = 0.01, OR = 0.73), both models adjusted by age.

**Conclusions:** this study demonstrates a relation between HOMA-IR and $PO_2$. Our results suggest that $PO_2$ could be a protective factor against insulin resistance.

**Key words:**

Cardiorespiratory fitness. Insulin resistance. Cardiopulmonary exercise test. Oxygen consumption. Obesity.

## Resumen

**Introducción:** la sensibilidad a la insulina ha sido ampliamente relacionada con el *fitness* cardiorrespiratorio (FCR), el cual puede ser evaluado a través del pulso de oxígeno ($PO_2$). Este corresponde al producto entre el volumen sistólico y la diferencia arteriovenosa de oxígeno y en sujetos sin alteraciones cardiovasculares podría ser un indicador de alteraciones del metabolismo a nivel periférico como la resistencia a la insulina (RI).

**Objetivo:** el objetivo del presente estudio es evaluar la relación entre el $PO_2$ y la RI en mujeres sedentarias con obesidad.

**Métodos:** cincuenta y cinco mujeres fueron sometidas a una prueba de ejercicio maximal para la evaluación del consumo máximo de oxígeno ($VO_{2max}$) y del $PO_2$. Los sujetos con un índice HOMA-IR mayor o igual a 2,5 fueron considerados con resistencia a la insulina. Los participantes fueron divididos en dos grupos, RI (n = 35) y no-RI (n = 20).

**Resultados:** el grupo RI presentó valores menores de $PO_2$ relativo al peso corporal (11,0 ± 1,7 *versus* 12,6 ± 1,4 ml·kg·latidos$^{-1}$, p = 0,001) y relativo a la masa libre de grasa (21,7 ± 2,9 *versus* 23,2 ± 2,8 ml·kg·latidos$^{-1}$, p = 0,038) respecto al grupo no-RI. No se encontraron diferencias estadísticamente significativas en el $VO_{2max}$ entre ambos grupos (no-RI = 1.53 ± 0.27 l·min$^{-1}$, RI = 1,51 ± 0,28 l·min$^{-1}$; p = 0,386). Se encontró una correlación inversa entre el $PO_2$ relativo al peso y el índice HOMA-IR (p < 0,001; r = -0,465). El análisis de regresión logística mostró una asociación entre el $PO_2$ relativo al peso (p = 0,001, OR = 0,47) y la masa libre de grasa (p = 0,01, OR = 0,73), ambos modelos ajustados por edad.

**Conclusiones:** este estudio demuestra que existe una relación entre el índice HOMA-IR y el $PO_2$. Estos resultados sugieren que el $PO_2$ podría ser un factor protector de RI.

**Palabras clave:**

*Fitness* cardiorrespiratorio. Resistencia a la insulina. Prueba de esfuerzo cardiopulmonar. Consumo de oxígeno. Obesidad.

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## INTRODUCTION

Obesity is a global pandemic associated with increased mortality, morbidity and a poor quality of life (1). Many authors suggest an inverse relationship between the adverse effects of obesity and cardiorespiratory fitness (CRF) (2,3).

Many studies have linked CRF with insulin sensitivity in both healthy and obese subjects (4,5). At the same time, CRF has been described as an independent and strong predictor of insulin sensitivity (6). An adequate evaluation of insulin sensitivity and CRF gives us accurate information about the health status of this group of patients (7).

Oxygen maximal consumption ($VO_{2max}$) is the gold standard in the evaluation of CRF. According to Fick's equation, the $VO_{2max}$ depends of stroke volume, heart rate and arteriovenous oxygen difference (a-$vO_2$ diff) (8).

In turn, oxygen pulse ($PO_2$) is defined as the total oxygen amount that can be extracted by the peripheral tissue in every heart beat (9) and has been inversely related to mortality risk in a more sensitive way than peak oxygen consumption in median age adults with cardiac insufficiency (10). In turn, the oxygen pulse ($PO_2$) is defined as the total oxygen amount that can be extracted by the peripheral tissue in every heart beat (9). $PO_2$ has been inversely related with a higher sensitivity to mortality risk over the peak oxygen consumption in median age adults with cardiac insufficiency (10). $PO_2$ is the product between stroke volume and a-$vO_2$ diff, therefore, in patients with cardiovascular disease it has been used as an indirect indicator of the stroke volume in maximal exercise intensities (11,12), assuming a normal arterial concentration of oxygen and a normal a-$vO_2$ diff (11). We propose that in subjects with normal values of stroke volume, the alterations in $PO_2$ could be an indicator of an impaired a-$vO_2$ diff.

$VO_{2max}$ and $PO_2$ depend on central and peripheral cardiovascular parameters. In the case of the $VO_{2max}$ the individual contribution of these variables is impossible to distinguish. However, if we assume a normal stroke volume, $PO_2$ could indicate a peripheral alteration of a-$vO_2$ diff, providing information about the metabolic compromise, evaluated through insulin sensitivity.

The goal of the present study is to evaluate the relation between $PO_2$ and IR in sedentary women with obesity.

## MATERIALS AND METHODS

### STUDY DESIGN

This was a retrospective study approved by the Ethics Committee with a waiver of the need to obtain informed consent (register 15-267). All participants' data was obtained from our database at Obesity Treatment Center according to inclusion/exclusion criteria.

### PATIENTS

Fifty-five women who met the criteria shown in figure 1, which were selected in a non-probabilistic way, were identified.

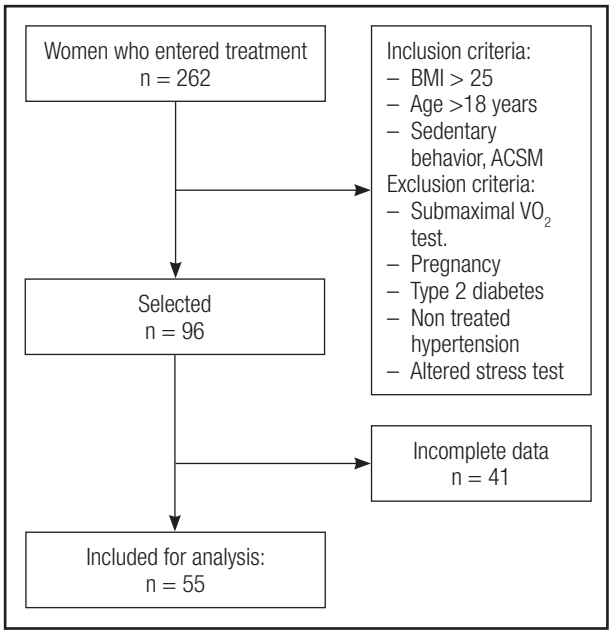


**Figure 1.**

Sample's selection flow chart (BMI: body mass index; ACSM: American College of Sports Medicine; $VO_2$: oxygen consumption).

### BODY COMPOSITION

Height was measured with a stadiometer (0.5 cm precision) and weight with a Seca® digital scale (0.1 kg precision). Both assessments were performed without shoes and in light clothing. Body mass index (BMI) was calculated as weight·height$^{-2}$ (kg·m$^{-2}$). Lean and fat mass, in kilograms, was assessed by using octopolar multi-frequency bioimpedance (InBody 720®) in a four-hour fasting state, without menstruation and with at least 12 hours free of exercise.

### CARDIORESPIRATORY FITNESS

An incremental cycle ergometer test was performed with gas analysis (Metalyzer 3B-R2, Cortex®). The participants were free of exercise, alcohol, coffee, drugs or other stimulant consumption in the previous 24 hours and in a six-hour fasting condition. Theoretical maximal load ($W_t$) was estimated by the Jones equation in watts (13). Protocol consisted of a three-minute rest period, then a three-minute warm up at 20% of $W_t$, followed by six-minute stages at 30, 40, 50 and 60% of $W_t$ until a respiratory exchange ratio (RER) ≥ 1 was reached. Then one-minute stages were performed with an increase 10% of $W_t$ until exhaustion. Verbal stimuli were allowed. The test was considered as maximal if a RER ≥ 1.1 was reached and/or if the maximal heart rate ($HR_{max}$) was greater or equal to the theoretical maximum predicted by the Morris equation for an ergometer cycle test (14). This protocol was adapted from the one proposed by Brun, Romain and Mercier (15).

The next variables were calculated from the average of the final 30 seconds from the last completed stage (breath by breath): $HR_{max}$ in beats·min$^{-1}$, maximal load in Watts ($W_{max}$), maximal load expressed as a percentage of $W_t$ ($W_{max(\%)}$) and relative to body weight in watts·kg ($W_{max\ rel}$).

The same methodology was used for determining CRF from the measurements of $VO_{2max}$. This was expressed as an absolute value in l·min$^{-1}$ and as a percentage of the maximum estimated ($VO_{2max(\%)}$), according to the Wasserman and Hansen weight algorithm (16). The peak oxygen pulse ($PO_2$) expressed in ml·beats$^{-1}$ and calculated as $VO_{2max}$·$HR_{max}^{-1}$, $PO_2$ relative to corporal weight ($PO_{2rel}$) calculated as $PO_2$·weight$^{-1}$ and the $PO_2$ relative to lean mass ($PO_{2rel\ lm}$) calculated as $PO_2$·lean mass$^{-1}$, both expressed in ml·kg·beats$^{-1}$. All percentage variations were calculated considering 100% of the group was non-insulin resistant (non-IR).

## INSULIN RESISTANCE

The homeostatic model assessment of insulin resistance (HOMA-IR), proposed by Mathews et al. (17), was used. Patients were considered as IR if they had a HOMA-IR value greater or equal to 2.5 according to the existent literature (18,19).

## STATISTICAL ANALYSIS

The sample was categorized into two groups according to the presence of IR (IR group and non-IR group). Distribution of the variables was assessed using the Kolmogorov-Smirnov test. Variables with normal distribution are presented as mean and standard deviation and those without normal distribution are shown as median and 25-75 percentile. For comparing means between both groups a Student's t-test for independent samples was used. In variables with normal distribution and in non-normally distributed variables, a Wilcoxon test was used. Since all the variables to be correlated had a non-parametric behavior, a Spearman correlation coefficient was used for correlations. For association of IR with oxygen pulse, a stepwise logistic regression analysis was performed, adjusted by age and BMI accordingly.

Data is presented as odds ratio and confidence interval of 95%. Goodness of fit was evaluated with a Hosmer-Lemeshow test. The significance level was set as $< 0.05$. Statistical analysis was performed with the computational statistics program STATA 12 (Stata Corp., College Station, TX).

# RESULTS

## BODY COMPOSITION

IR group presents a higher weight (81.5 [78.4-88.8] *vs* 73.4 [69.1-80.8] kilos, p = 0.004), BMI (32.8 [30.3-34.8] *vs* 29.0 [27.7-31.5], p = 0.001), fat mass (39.3 ± 7.5 *vs* 32.9 ± 8.3, p = 0.002) and body fat percent (46.7 ± 4.9 *vs* 42.8 ± 8.6, p = 0.020), and a lower lean mass percentage with respect to body weight (50.2% [46.8-53.1] *vs* 53.9% [51.7-57.4], p = 0.004) in contrast to the non-IR group. No differences were found between both groups in height (158.9 ± 5.7 *vs* 161.1 ± 7.6 cm, respectively) and in fat free mass (40.7 [39.3-45.9] *vs* 40.9 [37.8-44.1] kg, respectively).

## INSULIN RESISTANCE

The IR group showed higher values of HOMA (4.1 [3.2-5.8] *vs* 2.1 [2.0-2.5], p < 0.001), fasting glycaemia (87 [83-94] *vs* 84 [82-89] mg/dl, p = 0.044) and fasting insulinemia (19.2 [15.0-28.9] *vs* 10.2 [8.9-11.9] mg/dl, p < 0.001) in contrast to the non-IR group.

## CARDIORESPIRATORY FITNESS

Table I shows differences in CRF between both groups. The $VO_{2max\%}$ was a 7.1% lower in the IR group. At the same time, the $PO_{2rel}$ and the $PO_{2rel\ lm}$ were lower in the IR group in a 12.7% and a 6.5%, respectively. A negative correlation between HOMA-IR and $PO_{2rel}$ was also found (Fig. 2) in all the subjects. Table II shows logistic regression models for association of IR with $PO_2$, $PO_{2rel}$ and $PO_{2rel\ lm}$, adjusted by age. Models b) and c) were statistically significant and both are valid according to Hosmer-Lemeshow goodness of fit test (p = 0.446 and p = 0.289, respectively).

## DISCUSSION

In this study it was found that patients with insulin resistance had lower values of $PO_2$ relative to weight and lean mass. In addi-

**Table I.** Cardiorespiratory fitness

| | Non-IR (n = 20) | IR (n = 35) | p-value |
|---|---|---|---|
| $VO_{2max}$ (l·min$^{-1}$) | 1.53 ± 0.27 | 1.51 ± 0.28 | 0.386 |
| $VO_{2max(\%)}$ (%) | 83.2 ± 10.2 | 76.1 ± 11.9 | 0.015* |
| HRmax (bpm) | 161 ± 23 | 165 ± 17 | 0.212 |
| $PO_2$ (ml·beats$^{-1}$) | 9.59 ± 1.27 | 9.13 ± 1.33 | 0.111 |
| $PO_{2rel}$ (ml·kg·beats$^{-1}$) | 12.6 ± 1.4 | 11.0 ± 1.7 | 0.001* |
| $PO_{2rel\ lm}$ (ml·kg·beats$^{-1}$) | 23.2 ± 2.8 | 21.7 ± 2.9 | 0.038* |
| $W_{max}$ (W) | 108.3 ± 27.0 | 110.8 ± 24.1 | 0.360 |
| $W_{max\%}$ (%) | 88.1 ± 24.8 | 88.6 ± 17.7 | 0.460 |
| $W_{max\ rel}$ (W·kg$^{-1}$) | 1.40 ± 0.08 | 1.29 ± 0.06 | 0.317 |

*$VO_{2max}$: maximal oxygen consumption; $VO_{2max(\%)}$: percentage of the theoretical maximum oxygen consumption; $HR_{max}$: maximal heat rate; $PO_2$: maximal oxygen pulse; $PO_{2rel}$: maximal oxygen pulse relative to weight; $PO_{2rel\ lm}$: maximal oxygen pulse relative to lean mass; $W_{max}$: maximal workload; $W_{max\%}$: percentage of the theoretical maximum workload. $W_{max\ rel}$: maximal workload relative to weight. Values are expressed as mean (±) standard deviation. *Student's t-test for independent samples: p < 0.05.*

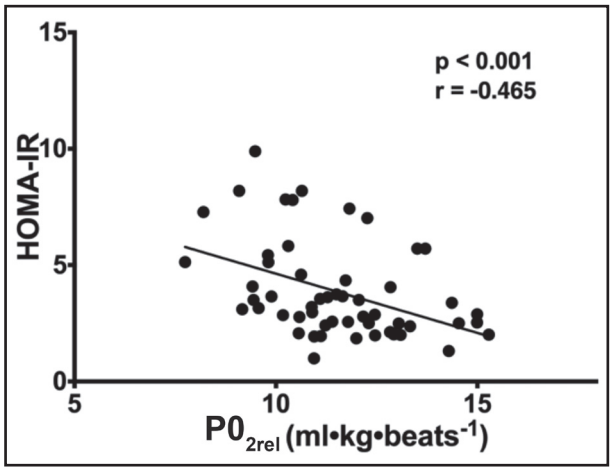


**Figure 2.**

Correlation between insulin sensitivity (HOMA-IR) and oxygen pulse relative to weight ($PO_{2rel}$) in all subjects.

**Table II.** Logistic regression for association of IR with $PO_2$

| Model | OR | 95% CI | p-value |
|---|---|---|---|
| a) $PO_2$ | 0.76 | 0.48-1.20 | 0.234 |
| b) $PO_{2rel}$ | 0.47 | 0.30-0.74 | 0.001* |
| c) $PO_{2rel\ lm}$ | 0.73 | 0.57-0.93 | 0.010* |

*OR: odds ratio; 95% CI: confidence interval of 95%; $PO_2$: maximal oxygen pulse; $PO_{2rel}$: maximal oxygen pulse relative to weight; $POM_{rel\ lm}$: maximal oxygen pulse relative to lean mass. *p-value < 0.05.*

tion, an association between these variables was observed that could indicate a possible protective role against IR.

Several studies have shown that patients with higher weights and BMI have higher stroke volumes (20,21). From this, if we consider that $PO_2$ depends directly on stroke volume and a-$vO_2$ diff (peripheral oxygen extraction during exercise) (8,9), the IR group (with higher weight and BMI) should have had higher $PO_2$ values. However, this was not the case and, when normalized by weight or fat free mass, the IR group presents lower values in comparison to the non-IR group.

The above could be explained considering that peripheral metabolic compromise is capable of nullifying the possible impact of stroke volume increase (related to weight) on $PO_2$, so there are no differences in net values. At the same time, if the values of $PO_2$ are normalized by weight or fat free mass, the impact of these variables on stroke volume and, in turn, on $PO_2$ are annulled, allowing to detect the impact of peripheral metabolism on this variable.

There are some articles that have related the decreases in muscle mitochondrial oxidative capacity with the decreases in muscle insulin sensitivity (22-25). These variations in mitochondrial metabolism could explain the decreases in peripheral oxygen utilization during exercise, although more studies are needed to verify this relationship.

From these results, $PO_2$ relative to weight or to fat free mass could be a useful parameter to estimate the peripheral metabolic status in patients with overweight and/or sedentary, whenever no stroke volume alterations exist. Further studies are necessary to elucidate the factors that allow us to differentiate the physiopathological context in which the $PO_2$ is a better reflex of the stroke volume or of the arteriovenous oxygen difference.

One of the main limitations of the study is the utilization of HOMA-IR instead of the hyperinsulinemic euglycemic clamp, which is considered as the gold standard for the determination of IR. In addition, it is necessary to evaluate the arteriovenous oxygen difference and stroke volume in these patients for a better understanding of the impact of these variables in the IR diagnosis. For future studies, it would be interesting to consider the variation in time of $PO_2$ and IR and to relate the variations of both variables after an exercise intervention.

## CONCLUSION

In conclusion, this study demonstrates a relation between IR and $PO_2$. Our results suggest that $PO_2$ could be a protective factor against insulin resistance. Further studies should be oriented to the treatment of IR through improvement in peripheral variables of physical fitness, such as $PO_2$. The evaluation of the impact of exercise in the $PO_2$ variations and their relationship with the improvements on insulin sensitivity is necessary.

## ETHICAL APPROVAL

This study was approved by the Scientific Ethics Committee (register 15-267). All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee.

## INFORMED CONSENT

A waiver of the need to obtain informed consent was obtained from Scientific Ethics Committee.

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