

# Cardiopulmonary Exercise Testing Contributes to Accurate Risk Assessment in Patients with Low-risk Pulmonary Hypertension

*La prueba cardiopulmonar de ejercicio contribuye a determinar con precisión el riesgo con precisión en pacientes con hipertensión pulmonar de bajo riesgo*

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## ABSTRACT

**Background:** European guidelines for pulmonary arterial hypertension (PAH) stratify the risk using clinical characteristics and complementary studies, including the cardiopulmonary exercise test (CPET). This takes into account 3 parameters: peak O<sub>2</sub> consumption (peak VO<sub>2</sub>), its percentage with respect to the predicted VO<sub>2</sub>, and the minute ventilation/carbon dioxide production (VE/VCO<sub>2</sub>) slope. However, none of the models that validated this way of stratifying risk included PCPE among their variables.

**Objectives:** To determine what proportion of patients with group I PAH considered to be at low risk and who walk >440 meters in the 6-minute walk test (6MWT) have parameters considered to be of moderate or high risk in the PCPE.

**Methods:** Patients >18 years of age, diagnosed with group I PAH at low risk of events, who walked >440 meters in the 6MWT and had NT-proBNP value < 300 pg/dL were included. A CPET was performed in which the peak VO<sub>2</sub>, its percentage with respect to the predicted VO<sub>2</sub>, and the VE/VCO<sub>2</sub> slope were recorded. It was determined what proportion of patients presented these parameters in a higher than low risk stratum (peak VO<sub>2</sub> consumption ≤15 ml/min/Kg, its percentage with respect to the predicted VO<sub>2</sub> ≤65% and the VE/VCO<sub>2</sub> slope ≥ 36).

**Results:** Eighteen patients were included. Despite being low-risk patients with a good functional class, all patients presented a peak VO<sub>2</sub> less than 85% of predicted, which determines a deterioration of functional capacity. A single patient (6%) presented the three parameters evaluated at low risk, 8 patients (44%) had at least one altered parameter, 7 patients (39%) presented 2 altered parameters and in 2 patients (11%) all parameters were altered. The parameters that were most frequently altered were the percentage of predicted peak VO<sub>2</sub> and the VE/VCO<sub>2</sub> slope in 67% of the cases. Only 4 patients presented a peak VO<sub>2</sub> <15 ml/kg/m. No patient presented peak VO<sub>2</sub> values or percentage of predicted VO<sub>2</sub> in the high-risk category. However, 6 patients (33%) presented a high-risk VE/VCO<sub>2</sub> slope.

**Conclusion:** Majority (92%) of the patients considered low risk and who walk more than 440 meters in 6 minutes presented at least one altered variable in the CPET. The VE/VCO<sub>2</sub> slope and the percentage of predicted peak VO<sub>2</sub> consumption were the most frequently altered variables. The VE/VCO<sub>2</sub> slope was the only one that showed values considered high risk. CPET could have a place in the precision stratification of low-risk patients. The value of this finding should be evaluated in prospective studies.

**Key words:** Hypertension, Pulmonary - Risk Assessment - Oxygen Consumption - Exercise Tolerance - Exercise Test

## RESUMEN

**Introducción:** Las guías europeas de hipertensión arterial pulmonar (HAP) estratifican el riesgo valiéndose de características clínicas y estudios complementarios entre los cuales está la prueba cardiopulmonar de ejercicio (PCPE), de la cual toma en cuenta 3 parámetros: el consumo de O<sub>2</sub> (VO<sub>2</sub>) pico, su porcentaje respecto del predicho y la pendiente ventilación minuto/ producción de dióxido de carbono (VE/VCO<sub>2</sub>). Sin embargo, ninguno de los modelos que validaron esta forma de estratificar el riesgo incluyeron la PCPE entre sus variables.

**Objetivos:** Determinar qué proporción de pacientes con HAP del grupo I considerados de bajo riesgo y que caminan >440 metros en la prueba de caminata de 6 minutos (PC6M) tienen en la PCPE parámetros considerados de riesgo moderado o alto.

**Material y métodos:** Se incluyeron pacientes > 18 años con diagnóstico de HAP del grupo I considerados de bajo riesgo con una PC6M > 400 metros a los que se les realizó una PCPE en la que se registró el VO<sub>2</sub> pico, su porcentaje respecto del VO<sub>2</sub> predicho y la pendiente VE/VCO<sub>2</sub>. Se determinó qué proporción de pacientes presentaban estos parámetros en un estrato de riesgo mayor a bajo riesgo (VO<sub>2</sub> pico < 15 ml/kg/min, su porcentaje respecto del predicho < 65% y la pendiente VE/VCO<sub>2</sub> >36).

**Resultados:** Se incluyeron 18 pacientes. A pesar de ser pacientes de bajo riesgo y con buena clase funcional todos presentaron un VO<sub>2</sub> pico menor al 85% del predicho, lo cual determina un deterioro al menos leve de la capacidad funcional. Un único paciente (6%) presentó los tres parámetros evaluados en bajo riesgo, 8 pacientes (44%) tuvieron al menos un parámetro alterado, 7 pacientes (39%)

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presentaron 2 parámetros alterados y en 2 pacientes (11%) todos los parámetros estuvieron alterados. Los parámetros que más frecuentemente se vieron alterados fueron el porcentaje respecto del  $\text{VO}_2$  predicho y la pendiente  $\text{VE}/\text{VCO}_2$ , en el 67% de los casos. Solo 4 pacientes presentaron un  $\text{VO}_2$  pico < 15 ml/k/m. Ningún paciente presentó valores de  $\text{VO}_2$  pico o porcentaje respecto del predicho en la categoría de alto riesgo. Sin embargo, 6 pacientes (33%) presentaron una pendiente  $\text{VE}/\text{VCO}_2$  considerada de alto riesgo.

**Conclusión:** El 94% de los pacientes considerados de bajo riesgo presentaron al menos una variable en la PCPE que no corresponde un perfil de riesgo bajo. La pendiente  $\text{VE}/\text{VCO}_2$  y el porcentaje de  $\text{VO}_2$  pico respecto del predicho fueron las variables más frecuentemente alteradas. La pendiente  $\text{VE}/\text{VCO}_2$  fue la única que mostró valores considerados de alto riesgo. La PCPE podría tener un lugar en la estratificación de precisión de pacientes de bajo riesgo. El valor de este hallazgo deberá ser evaluado en estudios prospectivos, al tiempo que genera las bases para el planteo de hipótesis respecto de la estratificación de riesgo y la intensidad del tratamiento en pacientes que aparentan estar en bajo riesgo.

**Palabras clave:** Hipertensión Pulmonar - Medición de Riesgo - Consumo de Oxígeno - Prueba de Esfuerzo - Tolerancia al Ejercicio

## INTRODUCTION

In 2015, the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines proposed a multiparametric tool of risk stratification to estimate the prognosis of patients with pulmonary arterial hypertension (PAH) and guide treatment strategies. These recommendations suggest classifying patients as low (mortality risk estimation <5% at 1 year), intermediate (mortality risk estimation between 5-10% at 1 year) and high (>10% mortality risk estimation at 1 year) risk, using clinical, imaging, and hemodynamic variables and estimation of aerobic capacity, which are known to be associated with patient prognosis. Among the latter, guidelines suggest using the World Health Organization (WHO) functional capacity (FC), the six-minute walking test (6MWT) and oxygen consumption ( $\text{VO}_2$ ) assessment in cardiopulmonary exercise testing (CPET). (1) This risk evaluation tool in PAH was retrospectively validated with different methods by three groups of investigators. The three validation models demonstrated an adequate capacity to discriminate patient prognosis. However, regardless of the method used, no group considered the use of CPET or  $\text{VO}_2$  assessment, employing only the WHO FC and 6MWT, (2-4) which represents a limitation, as both the FC and 6MWT present a prognostic performance inferior to CPET. (5,6) Firstly, there is no standardized way of assessing FC, a subjective parameter which reflects in the high interobserver variability in its evaluation, and the poor correlation between FC and maximum  $\text{VO}_2$ . (7,8) The 6MWT also presents several limitations: it is influenced by age, body mass index, presence of comorbidities, (9) has little correlation with hemodynamic variables, (10) the changes in the distance walked are not translated into modifications in the prognosis, (11,12) there is a “learning” effect, (13) and above all, it has a “ceiling” effect which determines its poor sensitivity in low-risk patients. (14)

The objective of our study was to establish what proportion of low-risk patients with PAH in FC I or II and who walk >440 meters in the 6MWT present moderate or high-risk parameters in CPET.

## METHODS

### Variable design and definition

A multicenter cross-sectional study was carried out including patients  $\geq 18$  years with PAH, in agreement with the 2015 ESC/ERS guideline definition, (1) who were at low-risk ac-

ording to the simplified risk evaluation method of the French registry: FC I-II, NT-proBNP <300 pg/mL and 6MWT >440 meters. (4) Patients with congenital diseases were excluded from the study.

The CPET was performed in a treadmill (H/P Cosmos, Mercury Med, Germany) within 90 days following risk stratification and the respiratory gas exchange was continuously analyzed (Cosmed Quark CPET OMNIA 1.6/7 software). A Bruce or modified Bruce protocol was used, selected by the operator according to the clinical conditions of the patient. Dynamic electrocardiographic changes (ST depression >1 mm) and arrhythmia occurrence were reported. The recorded variables included heart rate (HR), blood pressure, peripheral arterial oxygen saturation ( $\text{SaO}_2$ ),  $\text{VO}_2$ , rate of carbon dioxide production ( $\text{VCO}_2$ ) and minute ventilation (VE). The respiratory quotient or respiratory exchange ratio ( $\text{RER} = \text{VCO}_2 / \text{VO}_2$ ) was used as indicator of maximum exercise. Maximum exertion was considered for  $\text{RER} > 1.1$ . Peak  $\text{VO}_2$  was defined as average  $\text{VO}_2$  during the last minute of exercise and was expressed as milliliters/minute/kilogram of body weight (ml/min/kg), and was also reported as percentage of the predicted  $\text{VO}_2$  value (according to prespecified tables which take into account sex, age and body surface area). Functional capacity was defined as normal when peak  $\text{VO}_2$ /predicted  $\text{VO}_2$  was  $\geq 85\%$ . The three variables considered for PAH risk evaluation in the ESC guideline were: (1) peak  $\text{VO}_2$ , its percentage with respect to predicted  $\text{VO}_2$  and the  $\text{VE}/\text{VCO}_2$  slope. The proportion of patients presenting these parameters in a risk category above low was established (peak  $\text{VO}_2 \leq 15$  ml/min/kg, percentage with respect to predicted  $\text{VO}_2 \leq 65\%$  and a  $\text{VE}/\text{VCO}_2$  slope  $\geq 36$ ).

### Statistical analysis

Categorical variables were expressed as frequency and percentage, and were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were expressed as mean and standard deviation, or median and interquartile range (IQR), according to their distribution. Student's t test or the Wilcoxon rank sum test was used to compare two groups, as appropriate. Statistical significance was considered for  $p < 0.05$ . Stata 13.0 software package was used for statistical analyses.

### Ethical considerations

The study was performed following the recommendations for medical research stated in the Declaration of Helsinki, Good Clinical Practice standards and current ethical regulations. The protocol was reviewed and approved by the Ethical Committees of the participating centers.

## RESULTS

A total of 18 patients were included in the study and 16 (89%) were women. Median age was 43.5 years

(IQR 33-51 years) and median time from diagnosis to evaluation was 4.7 years (IQR 1.8-8.6 years). In half of the cases (n=9) the etiology of HAP was idiopathic, in 6 cases it was associated with connective tissue disease, in 2 cases it was secondary to human immunodeficiency virus (HIV) and in one case to portal hypertension. Baseline population characteristics are described in Table 1.

All patients evaluated presented an exercise functional capacity below 85% of the predicted value (Table 2). Only one female patient presented the three parameters assessed in the low-risk level. Eight patients (44%) had at least one abnormal parameter, 7 patients (39%) presented 2 altered parameters and in 2 patients all the parameters were anomalous. The most frequently altered parameters were the percentage with respect to predicted  $VO_2$  and the  $VE/VCO_2$  slope in 67% of cases. Only 4 patients presented  $VO_2 < 15$  ml/kg/min. No patient evidenced peak  $VO_2$  or percentage of predicted  $VO_2$  values in the high risk category. However, 6 patients (33%) presented a  $VE/VCO_2$  slope considered as high risk (Figure 1).

## DISCUSSION

Despite having included a population of patients who at the time of CPET were at a low-risk level and with preserved functional capacity, all the patients evaluated presented a peak  $VO_2 < 85%$  of the predicted value, which indicates at least mild impairment of functional capacity. (15) Only one patient presented all the parameters evaluated within the low-risk profile. Surprisingly,

**Table 2.** Cardiopulmonary exercise testing results

|   |      |           |
|---|------|-----------|
| Peak $VO_2$ , ml/kg/min, median (IQR)           | 17,5 | (15.5-20) |
| Peak $VO_2$ /predicted $VO_2$ , %, median (IQR) | 60   | (56-66)   |
| $VE/VCO_2$ slope, median (IQR)                  | 39   | (33-49)   |
| Peak $VO_2 < 15$ ml/kg/min, n (%)               | 4    | (22%)     |
| Peak $VO_2$ /Predicted $VO_2 < 65%$ , n (%)     | 12   | (67%)     |
| $VE/VCO_2$ slope $> 36$ , n (%)                 | 12   | (67%)     |
| $VE/VCO_2$ slope $> 45$ , n (%)                 | 6    | (33%)     |
| N° of abnormal parameters                       |      |           |
| 0   | 1    | (6%)      |
| 1   | 8    | (44%)     |
| 2   | 7    | (39%)     |
| 3   | 2    | (11%)     |

IQR: Interquartile range;  $VO_2$ : oxygen consumption;  $VE/VCO_2$ : Minute ventilation/carbon dioxide production,

ly, this patient was a woman treated with three drugs: phosphodiesterase-5 inhibitor, endothelin receptor antagonist, and intravenous prostanoid, which were started simultaneously in the context of cardiogenic shock 30 months prior to this evaluation. Although this evolution would seem unexpected, it is consistent with the results recently published by Boucly et al., who report a 5-year survival of 91% in 76 high-risk patients who were treated with initial triple therapy, including a parenterally administered prostanoid. (16)

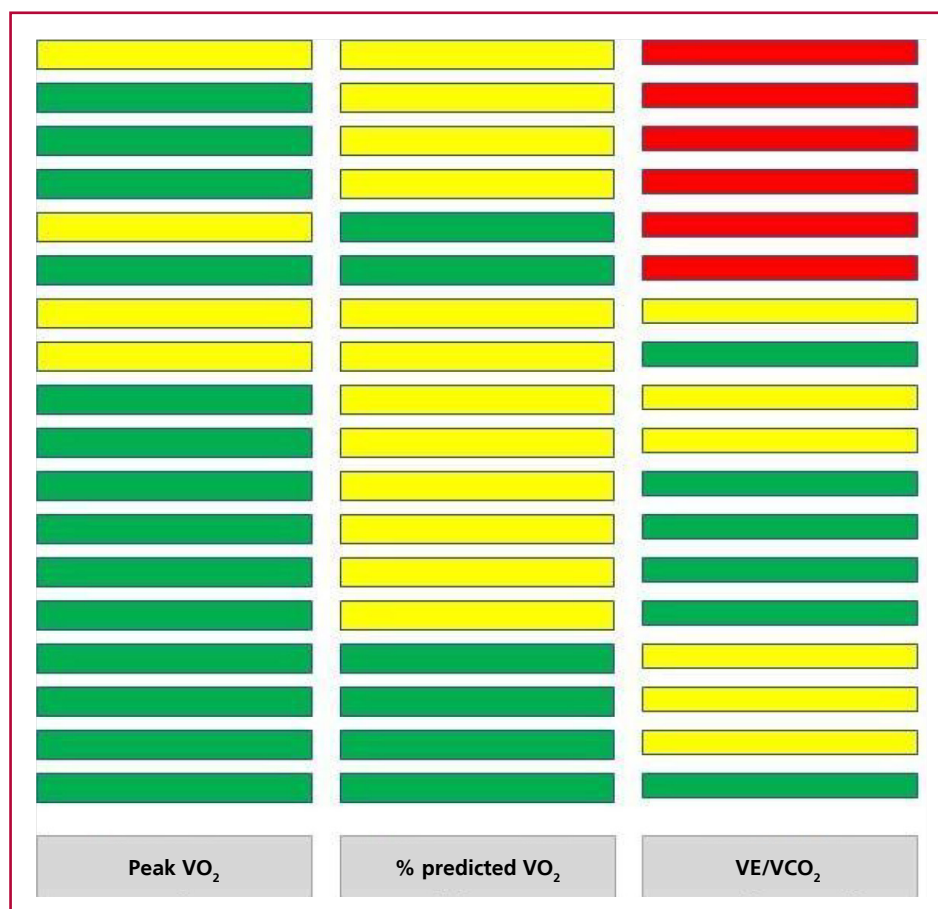
The rest of the patients (92%) presented at least one altered parameter in CPET. This may be due to the inherent limitations of FC assessment and the diagnostic sensitivity of the 6MWT. The population of our study was significantly younger than the low-risk population of the European registries in which the risk stratification proposed by the ESC/ERS guidelines was validated: median age of 43.5 years vs. mean of  $52 \pm 17$  years in the German registry; mean of  $57 \pm 17$  years in the French registry and median of 57 (IQR 39-68) years in the Swedish registry. (2-4) The fact that the patients are younger may affect the sensitivity of the 6MWT to detect FC impairment. (14) In the same sense, the fact that patients have several years of disease evolution and therefore have performed the 6MWT on repeated occasions can generate a "learning" effect that conditions its diagnostic capacity. (13)

Recent publications have sought to subdivide the moderate-risk population into two strata: moderate-low and moderate-high risk. (17) Even Badagliacca et al. demonstrated and validated the value of CPET in the substratification of moderate-risk patients. (18) This substratification has important implications when making therapeutic decisions, both pharmacological as in time of inclusion on the lung transplantation list. (19) However, and despite the fact that low-risk patients present a non-negligible rate of events, as the 5-year mortality in the Swedish, French, and German registries was 8%, 9% and 31.9% respectively, (2-4) little has been done to identify which patients considered to be at low risk are more likely of disease

**Table 1.** Baseline variables (n=18)

|   |                |
|---|----------------|
| Female sex, n (%)                       | 16 (89)        |
| Age, years, median (IQR)                | 43.5 (33-51)   |
| Functional class, n (%)                 |                |
| I                                       | 4 (22)         |
| II                                      | 14 (78)        |
| Etiology, n(%)                          |                |
| Idiopathic                              | 9(50)          |
| CTD                                     | 6(33)          |
| HIV                                     | 2 (11)         |
| Portopulmonary                          | 1(6)           |
| 6MWT, m. median (IQR)                   | 484 (465-510)  |
| NT-proBNP, pg./mL, median (IQR)         | 116 (59-272)   |
| MPAP, mmHg, median (IQR)                | 41 (33-50)     |
| RAP, mmHg, median (IQR)                 | 6 (4-8)        |
| PVR, Wood units, median (IQR)           | 7.6 (4.7-8.9)  |
| CI, L/min/m <sup>2</sup> , median (IQR) | 2.85 (2.4-3.2) |
| N° drugs, n (%)                         |                |
| 1                                       | 1(11)          |
| 2                                       | 12(67)         |
| 3                                       | 4 (22)         |

6MWT: 6-minute walking test; CI: Cardiac index; CTD; Connective tissue disease; HIV: Human immunodeficiency virus; IQR: Interquartile range; MPAP: Mean pulmonary artery pressure, PVR: Pulmonary vascular resistance; RAP: Right atrial pressure, .



**Fig. 1.** Graphic distribution of variables considered in cardiopulmonary exercise testing according to the risk category of the 2015 ESC/ERS guidelines. (1)

Red: high risk; Yellow: intermediate risk; Green: low risk; VO<sub>2</sub>: O<sub>2</sub> consumption; VE: Minute ventilation; VCO<sub>2</sub>: CO<sub>2</sub> production

progression and even of suffering fatal events. Similarly, the lowest mortality, 8% at 5 years, reported by the Swedish registry, does not seem at all auspicious if we consider that our population had an average age of 43 years. The CPET is then seen as a very useful tool to better identify those patients at higher risk who require a more aggressive treatment strategy with triple therapy and/or parenteral drug administration.

A recent study analyzed the mortality of incident patients diagnosed with PAH according to whether they started treatment before or after the publication of the 2015 ESC/ERS guidelines, which advocate the initiation of treatment with two drugs. (20) Although the investigators found that as of 2015 the percentage of patients who started combination treatments had significantly increased, this did not translate into a reduction of mortality; nevertheless, what was associated with lower mortality was reaching a low-risk stratum. In this same sense, although our work does not allow us to draw definitive conclusions, it can hypothesize about the importance of reaching a state of "absolute low risk". We understand as such, an exhaustive risk assessment strategy based on a method that allows FC to be estimated in an objective, measurable, reproducible manner that is correlated with hemodynamic parameters and whose variations correlate

with the prognosis of the disease, such as CPET. (5,6)

Another clinical scenario of potential value for CPET concerns those patients who, thanks to treatment, have reached a low-risk state and for some reason the possibility of de-escalating treatment is being considered. Although, in principle, we do not believe that there is any valid situation that warrants de-escalating treatment when the objective, that is so difficult to achieve, has been reached, it is not unusual for this possibility to be raised, both in the literature and in daily practice. (21,22). In this sense, CPET could establish if the patient really has a preserved FC prior to the start of medication reduction and could detect a possible deterioration of the FC before it is clinically manifest. However, and mindful of the presence of studies that show that patients who worsened their condition by reducing the intensity of treatment do not recover the lost well-being when a rescue treatment is administered, we strongly advise against venturing to reduce the intensity of treatment if no serious adverse effects occur. (23).

Our work has multiple limitations. In the first place, it is a small sample due to the fact that we are analyzing a disease considered rare, where most of the patients present at moderate or high-risk levels, and less than 30% are in FC I or II. (2-4) Secondly, al-

though these are all patients who have been diagnosed a while ago, there is a great dispersion regarding the time of disease development. Another point that deserves to be mentioned is the heterogeneity that exists in terms of treatment. Although 12 patients (67%) are being treated with 2 drugs (an endothelin receptor antagonist and a 5-phosphodiesterase inhibitor), 2 are treated with 1 alone, and 4 with 3 drugs: 2 with selexipag, 1 with intravenous epoprostenol and 1 with subcutaneous treprostinil. This treatment heterogeneity suggests that, although they are patients with different evolutionary stages, it does not rule out the hypothesis underlying this study, which does not intend to compare one patient with another directly, but rather the possibility of disease progression with the consequent need to eventually require a more aggressive treatment, either pharmacological or a transplant, according to the baseline treatment.

### CONCLUSIONS

All except one of the patients considered as low risk and who walk more than 440 meters in 6 minutes, presented at least one altered variable in CPET. The VE/VCO<sub>2</sub> slope and the percentage of predicted O<sub>2</sub> consumption were the most frequently altered variables. The VE/VCO<sub>2</sub> slope was the only one that showed values considered as high risk. The CPET could have a place in the substratification of low-risk patients and thus allow the identification of a stratum of "absolute low risk". The importance of reaching this level of "absolute low risk" in terms of prognosis and patient survival should be evaluated in prospective studies.

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