



Lack of concordance between the different exercise test measures used in the risk stratification of patients with pulmonary arterial hypertension

Víctor M. Mora Cuesta¹  | Amaya Martínez Meñaca¹  |
David Iturbe Fernández¹  | Sandra Tello Mena¹ | Pilar Alonso Lecue²  |
Daniel Fernández Márquez¹ | Begoña Sáinz-Ezquerro Belmonte¹ |
María José Gallardo Ruiz¹ | José Manuel Cifrián Martínez¹ 

¹Respiratory Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain

²Instituto de Investigación Valdecilla (IDIVAL), Santander, Spain

Correspondence

Víctor M. Mora Cuesta, Respiratory Department, Hospital Universitario Marqués de Valdecilla, Avda. Valdecilla s/n. 39003, Santander, Cantabria. Spain.
Email: victormanuel.mora@scsalud.es

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Abstract

In pulmonary arterial hypertension (PAH) patients it is essential to perform a prognostic assessment to optimize the treatment. The aim of this study is to evaluate the risk stratification concordance assessed with different exercise test variables in a cohort of PAH patients. A retrospective analysis was performed using patient data registered in the PAH unit. Only those patients in whom the mean time elapsed between the 6-min walking test (6MWT) and the cardiopulmonary exercise test (CPET) was a maximum of 6 months were selected. A total of 140 records from 40 patients were finally analyzed. When it came to assessing the concordance between the two exercise tests in the guidelines (CPET and 6MWT), up to 84.3% of the records did not coincide in terms of the risk stratification. Exclusively considering the CPET parameters, most of the records (75%) failed to include all three variables in the same risk category. When analyzing the VO_2 alone, up to 40.7% of the tests yielded different risk classifications depending on whether the parameter was expressed. In conclusion, there is a low concordance between the two proposed exercise tests. These results should be a call for reflection on whether the cut-off points set for the exercise tests proposed for the current risk stratification are adequate to achieve a correct risk stratification or whether they require an appropriate revision.

KEYWORDS

cardiopulmonary exercise test, pulmonary arterial hypertension, risk assessment, 6-min walking test

Abbreviations: 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; ERS, European Respiratory Society; ESC, European Society of Cardiology; PAH, pulmonary arterial hypertension; VO_2 , Oxygen uptake.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a subtype of precapillary pulmonary hypertension (PH) characterized by small-caliber pulmonary arteries remodeling, which causes a progressive increase in vascular resistance and, at advanced stages, results in right heart failure and death.¹ Although recent advances in the treatment of PAH have managed to increase patient survival, it is still an incurable disease.

In PAH patients, it is essential to perform a prognostic assessment, both at the time of diagnosis and throughout their follow-up, to optimize the condition's treatment.² This assessment is complex, since no single variable provides sufficient prognostic information. Therefore, several strategies have been developed in recent years to assess the risk of PAH patients, such as those proposed by the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines on the diagnosis and treatment of PH, as well as the risk calculator of the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL). The recently published 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension maintain the same concept of risk assessment at diagnosis and during follow-up.³

The ESC/ERS 2015 guidelines proposed a risk scale that includes clinical and functional criteria, imaging tests, analytical determinations, and hemodynamic variables. Based on these variables, patients can be classified into three groups according to their 1-year mortality risk: low risk (1-year mortality <5%), intermediate risk (1-year mortality of 5%–10%), and high risk (1-year mortality >10%). The new 2022 guidelines keep this model at the time of diagnosis, adding some new imaging parameters (cardiac resonance, echocardiogram), and hemodynamic parameters (stroke volume index). However, it maintains the same cut-off points for the variables of the cardiopulmonary exercise test (CPET) and for the 6-min walk test (6MWT).

Three abbreviated versions of the model have been evaluated in retrospective cohorts of patients with recurring PAH ever since this risk stratification strategy was published. The French group's model proposes two simplified approaches, an invasive and a noninvasive one, using only some of the variables proposed in the ESC/ERS guidelines.⁴ Both the Swedish method and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) use a similar strategy, whereby scores from 1 to 3 are assigned to each variable (1 = low risk; 2 = intermediate risk; 3 = high risk) and a rounded mean of these scores defines the risk group to which a patient belongs.^{5,6}

All these models have demonstrated their prognostic validity by simplifying the number of variables used. It should be noted that these stratification models do not assess the imaging study variables included in the original model of the ESC/ERS 2015 guidelines (right atrial area or the presence of pericardial effusion as determined by an echocardiogram/magnetic resonance imaging scan) or the variables obtained from the CPET.

Moreover, the REVEAL risk stratification model and its updated version, REVEAL 2.0, are also available and, unlike the European scale, this model includes non-modifiable variables, including the type of PAH, as well as the patient's age and comorbidities, such as an impaired kidney function, among others. Furthermore, with this approach, the different variables are assigned different weights when it comes to calculating the mortality risk, obtaining a definitive, final score. The REVEAL 2.0 update has now been validated in a cohort of PAH patients in New Zealand.^{7,8}

Given that several recent studies have demonstrated the usefulness of different parameters measured by the CPET in both the diagnosis and prognosis of PAH, these were included in the latest 2022 ERS/ESC guidelines. However, although it is a useful, safe, and noninvasive test, neither the simplified approaches nor the REVEAL model use variables from the CPET and, most times, the distance covered during the 6MWT is used as an exercise test parameter.

The aim of this study is to evaluate the risk stratification concordance assessed with different exercise test variables in a cohort of PAH patients.

MATERIALS AND METHODS

To carry out this study, a retrospective analysis was performed using patient data registered in a PH unit of a reference center for lung transplantation, interstitial lung diseases, and pulmonary hypertension, from January 2016 through October 2021. The study was approved by the local ethics. Informed consent was obtained from all subjects involved in the study.

According to the 2015 ERS/ESC international guidelines for the diagnosis and treatment of PAH, it is advisable to perform a CPET and hemodynamic testing every 6–12 months. Based on this recommendation, because this study aims to assess the concordance between the different exercise tests (6MWT and CPET), only those patients in whom the mean time elapsed between the 6MWT and the CPET was a maximum of 6 months were selected, and those in which there were no changes in the treatment between the performance of both tests.

The risk assessment was determined according to the recommendations of the ESC/ERS 2015 guidelines, classifying the patients into low risk (1-year mortality <5%), intermediate risk (1-year mortality of 5%–10%), or high risk (1-year mortality >10%) based on the cut-off points set for each parameter.

Among all patient records selected, those that did not report all exercise test values (distance covered during the 6MWT, oxygen [O₂] uptake in ml/kg/min, O₂ uptake expressed as a percentage, and the relation between the minute ventilation and the carbon dioxide output [VE/VCO₂]) were excluded. The reference values used to calculate oxygen uptake were those of Wasserman. All 6MWT were performed at the same site by the same personnel. Furthermore, all CPETs were performed on the same equipment and evaluated by the same physician. To be able to compare two tests carried out by the same patient, the same exercise protocol used in the previous ones was used for the successive tests. Both 6MWT and CPET were performed without supplemental oxygen.

Statistical analysis

The IBM SPSS Statistics 20 software was used to perform the statistical analysis. Continuous quantitative variables with a normal distribution were expressed as a mean \pm standard deviation and those with an abnormal distribution were expressed as a median and an interquartile range. Categorical variables were expressed as frequencies and percentages. The Kolmogorov–Smirnov test was used to determine whether continuous quantitative variables had a normal or abnormal distribution. Cohen's kappa statistic was used to quantify intertest agreement.

A p value ≤ 0.05 was considered statistically significant for all analyses.

RESULTS

From the initial 186 records available, 46 were excluded because there was a difference of more than 6 months between CPET and 6MWT from January 01, 2016, to October 07, 2021. Thus, a total of 140 records from 40 patients were finally analyzed (shown in Figure 1).

Each of these 40 patients had completed a median of three¹⁻⁵ CPET, with a minimum of one completed test and a maximum of nine. The mean age at the time of diagnosis was 42.57 ± 13.05 years, and most patients were female (67.5%). The majority of cases of PAH were of hereditary (22.5%) and idiopathic etiology (20%), although others were associated with congenital heart disease (10%) or connective tissue diseases (20%), among others (Table 1).

The median time elapsed between the 6MWT and the CPET in the 140 exercise test records available was 84 (47–98) days (Table 2). At the time of the exercise testing, 95.7% of the patients were receiving specific treatment for PAH: 13.6% with oral monotherapy, 38.6% with dual oral therapy, 17.9% with triple oral therapy, and 22.9% with oral therapy and parenteral therapy.

At the time the CPET was performed, 32.1% of the patients fell within functional class I of the World Health Organization (WHO), 55.0% fell within functional class II, 12.9% fell within functional class III, and no patient was in functional class IV (Table 3). The mean distance covered by these patients during the 6MWT was 498.04 ± 98.55 m. As for the CPET values, the mean O₂ consumption (VO₂) was 16.58 ± 4.61 ml/kg/min or

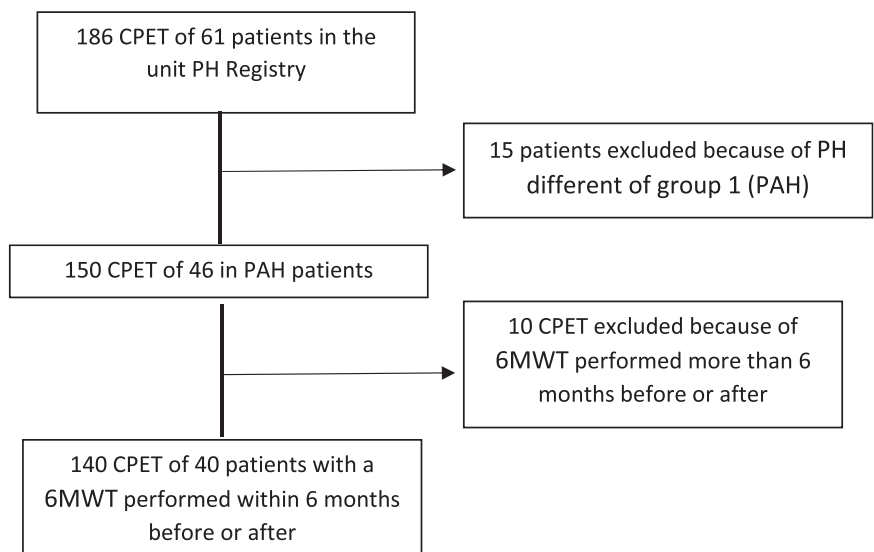


FIGURE 1 Flowchart of patients and risk assessments included in the study. 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension.

TABLE 1 Baseline characteristics of the patients Included in the study

| N | 40 |
|-----------------------------|---------------------|
| Sex | |
| Male | 13 (32.5%) |
| Female | 27 (67.5%) |
| Age at diagnosis | 42.57 ± 13.05 years |
| Type of PAH | |
| Hereditary | 9 (22.5%) |
| Idiopathic | 8 (20%) |
| Connective tissue disease | 8 (20%) |
| Veno-occlusive | 5 (12.5%) |
| Congenital heart disease | 4 (10%) |
| Portopulmonary hypertension | 4 (10%) |
| HIV | 1 (2.5%) |
| Drugs or toxins | 1 (2.5%) |

Abbreviations: HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

63.63% ± 18.10% of the theoretical value, and the median VE/VCO₂ was 38.8 (35.3–46). Remaining CPET values are summarized in Table 3. Concerning the hemodynamic variables, 41.42% of the CPET episodes had a cardiac catheterization done close to CPET (less than 6 months), with a time elapsed between CPET and right heart catheterization of 70 (26–186.25) days. The cardiac catheterization data are summarized in Table 3.

According to the cut-off points established by the 2015 ERS/ESC guidelines, based on their functional class, 87.1% of the patients would be at low risk, 12.9% at intermediate risk, and no patients at high risk. Based on the results of the 6MWT, 72.9% of the patients were at a low risk, 27.1% at an intermediate risk, and no patients at a high risk. In turn, according to the results of the CPET based on the VO₂ measured in ml/kg/min, 63.6% of the patients were at a low risk, 24.3% at an intermediate risk, and 12.1% at a high risk. However, when the VO₂ was expressed as a percentage, 44.3% of the patients were at a low risk, 50.7% were at an intermediate risk, and 5.0% were at a high risk. Regarding the VE/VCO₂, 29.3% of the patients were at a low risk, 39.3% were at an intermediate risk, and 31.4% were at high risk (Table 4).

When it came to assessing the concordance between the two exercise tests contemplated in the guidelines (CPET and 6MWT), up to 84.3% of the records did not coincide in terms of the risk stratification within the same group; that is, only 13.6% of the records included all variables (distance covered during the 6MWT and the

TABLE 2 Patients' situation at the time of the exercise testing

| N | 140 |
|--|-------------------|
| Time elapsed between the 6MWT and the CPET | 84 (47.5–98) days |
| Treatment at the time of the CPET | |
| No treatment | 6 (4.3%) |
| Calcium channel blockers | 2 (1.4%) |
| PDE-5 inhibitors | 119 (85.0%) |
| Riociguat | 4 (2.9%) |
| ERAs | 118 (84.3%) |
| Selexipag | 25 (17.9%) |
| Subcutaneous treprostinil | 11 (7.9%) |
| Intravenous treprostinil | 3 (2.1%) |
| Inhaled treprostinil | 3 (2.1%) |
| Intravenous epoprostenol | 17 (12.1%) |
| Treatment combinations at the time of the CPET | |
| No treatment | 6 (4.3%) |
| Oral monotherapy (PDE-5 inhibitors, Riociguat or ERAs) | 19 (13.6%) |
| Dual oral therapy (PDE-5 inhibitors or Riociguat + ERAs) | 54 (38.6%) |
| Triple oral therapy (PDE-5 inhibitors or Riociguat + ERAs + selexipag) | 25 (17.9%) |
| Dual oral therapy + parenteral therapy | 32 (22.9%) |
| Oral monotherapy + parenteral therapy | 2 (1.4%) |

Abbreviations: 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; ERA, endothelin receptor antagonist; PDE-5, phosphodiesterase-5.

three variables of the CPET) in the low-risk class and only 2.1% of them included all of these variables in the intermediate-risk class (Table 5).

Exclusively considering the CPET parameters, most of the records (75%) failed to include all three variables in the same risk category, with all three variables only being included in 15% of the records corresponding to a low-risk class, 6.4% of those corresponding to an intermediate risk class, and only 3.6% of those corresponding to a high-risk class.

When analyzing the VO₂ alone, up to 40.7% of the tests yielded different risk classifications depending on whether the parameter was expressed in ml/kg/min or a percentage.

Concordance between the variables used to measure exercise capacity (CPET, 6MWT, and functional class) was studied by the Cohen's kappa index. The degree of concordance between the different variables showed a fair or slight agreement. (Table 6).

TABLE 3 Risk stratification variables used

| | |
|---|---------------------|
| WHO functional class at the time of the CPET | |
| I | 45 (32.1%) |
| II | 77 (55%) |
| III | 18 (12.9%) |
| IV | 0 (0%) |
| 6MWT (meters) | 498.04 ± 98.55 |
| CPET | |
| VO ₂ (ml/kg/min) | 16.58 ± 4.61 |
| VO ₂ (%) | 63.63 ± 18.10 |
| Maximum load (watts) | 70 (60–98.75) |
| Maximum load (%) | 61 (49.25–76) |
| Anaerobic threshold for maximum VO ₂ (%) | 43.88 ± 13.46 |
| VE/MVV (%) | 72.97 ± 23.14 |
| Maximum heart rate (beats/minute) | 145.92 ± 14.46 |
| Maximum heart rate (%) | 84.98 ± 8.53 |
| O ₂ pulse (ml/beat) | 7.54 ± 2.49 |
| O ₂ pulse (%) | 73.75 ± 19.70 |
| RER | 1.14 ± 0.10 |
| VE/VCO ₂ | 38.80 (35.3–46) |
| Time elapsed between CPET and right heart catheterization | 70 (26–186.25) days |
| Catheterization before CPET | 60.3% |
| Catheterization after CPET | 39.7% |
| Cardiac catheterization | |
| Systolic PAP (mmHg) | 76.25 ± 28.31 |
| Diastolic PAP (mmHg) | 32.15 ± 14.52 |
| Mean PAP (mmHg) | 47.32 ± 17.74 |
| PWP (mmHg) | 10.82 ± 3.12 |
| RAP (mmHg) | 9.56 ± 4.99 |
| Cardiac output (L/min) | 4.74 ± 1.33 |
| Cardiac index (L/min/m ²) | 2.69 ± 0.74 |
| PVR (Wood units) | 9.12 ± 5.82 |

Abbreviations: 6MWT, 6-min walk test; CPET, cardiopulmonary exercise test; MVV, maximum voluntary ventilation; mmHg, millimeters of mercury; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; RAP, right atrial pressure; RER, respiratory exchange ratio; SvO₂, mixed venous oxygen saturation; VE, respiratory minute volume; VO₂, O₂ uptake; WHO, World Health Organization.

TABLE 4 Risk assessment according to different variables

| | Low risk (%) | Intermediate risk (%) | High risk (%) |
|-----------------------------|--------------|-----------------------|---------------|
| WHO functional class | 87.1 | 12.9 | 0 |
| Exercise tests | | | |
| 6MWT | 72.9 | 27.1 | 0 |
| VO ₂ (ml/kg/min) | 63.6 | 24.3 | 12.1 |
| VO ₂ (%) | 44.3 | 50.7 | 5.0 |
| VE/VCO ₂ | 29.3 | 39.3 | 31.4 |
| Catheterization | | | |
| RAP | 33.9 | 58.9 | 7.1 |
| Cardiac index | 59.6 | 17.3 | 23.1 |

Abbreviations: 6MWT, 6-min walk test; RAP, right atrial pressure; SvO₂, mixed venous oxygen saturation; VO₂, O₂ uptake; WHO, World Health Organization.

DISCUSSION

Risk stratification has become a fundamental tool in the initial evaluation and follow-up of patients with PAH. Different strategies such as the REVEAL model, its updated version, REVEAL 2.0, or the 2015 ERS/ESC guidelines approach have demonstrated their usefulness in predicting the risk of 1-year mortality. However, the results of this study demonstrate the need to reestablish the cut-off points of certain variables as a result of the discordance in the risk classification determined by similar tests, such as the CPET and the 6MWT, which evaluate the patients' exercise capacity, as well as the discrepancies in the risk classification obtained with the same test, such as the CPET, or even the same variable, such as VO₂.

Because of the need for assessing multiple parameters, which cannot always be collected during all patient visits, different simplified approaches have been developed, such as those proposed by the French registry, COMPERA, or the Swedish registry, all of which have shown that the risk can be classified reliably using fewer parameters. Subsequently, the researchers from the COMPERA registry demonstrated the usefulness of a simplified risk assessment using functional class, 6MWT, and NT-proBNP or BNP, but this time divided into four strata (low risk, intermediate-low risk, intermediate-high risk, and high risk).⁹ This model was validated in the French registry cohort.¹⁰ According to this evidence, in the recent 2022 guideline this risk assessment has been

TABLE 5 Risk assessment according to different exercise variables

| | All variables in the low-risk group (%) | All variables in the intermediate-risk group (%) | All variables in the high-risk group (%) | Risk assessments with variables in different risk groups (%) |
|----------------------------------|---|--|--|--|
| 6MWT + CPET | | | | |
| Distance covered during the 6MWT | 13.6 | 2.1 | 0 | 84.3 |
| VO ₂ (ml/kg/min) | | | | |
| VO ₂ (%) | | | | |
| VE/VCO ₂ | | | | |
| CPET variables | | | | |
| VO ₂ (ml/kg/min) | 15 | 6.4 | 3.6 | 75 |
| VO ₂ (%) | | | | |
| VE/VCO ₂ | | | | |
| VO ₂ (ml/kg/min or %) | 37.1 | 17.1 | 5 | 40.7 |

Abbreviations: 6MWT, 6-minute walk test; CPET, cardiopulmonary exercise test; VO₂, O₂ uptake.

| | Kappa value | p | 95% CI |
|---|-------------|--------|--------------|
| 6MWT and VO ₂ (ml/kg/min) | 0.317 | <0.001 | 0.183–0.451 |
| 6MWT and VO ₂ (%) | 0.087 | 0.200 | –0.041–0.215 |
| 6MWT and VE/VCO ₂ | 0.054 | 0.229 | –0.023–0.132 |
| VO ₂ (ml/kg/min) and VO ₂ (%) | 0.309 | <0.001 | 0.180–0.437 |
| VO ₂ (ml/kg/min) and VE/VCO ₂ | 0.139 | 0.007 | 0.038–0.240 |
| Functional class and VO ₂ (ml/kg/min) | 0.139 | 0.016 | 0.013–0.0247 |
| Functional class and VO ₂ (%) | 0.141 | 0.005 | 0.054–0.229 |
| Functional class and VE/VCO ₂ | 0.043 | 0.197 | –0.004–0.009 |
| Functional class and 6MWT | 0.264 | <0.001 | 0.090–0.438 |

Abbreviations: 6MWT, 6-minute walk test; VO₂, O₂ uptake.

TABLE 6 Concordance between different variables used to assess the risk group (low, intermediate, and high risk)

included in four strata for the follow-up of patients with PAH.

The results of the 6MWT and the CPET in terms of the exercise capacity assessment are assigned the same weight in the initial evaluation, and CPET in the 2022 guideline is not recommended in all follow-up risk assessments, it can only be considered in some cases. The 6MWT has been a widely used test in the assessment of PAH in different studies and the primary objective for the approval of certain drugs. In addition, it is a simple test to perform and interpret, is reproducible, and is associated with few risks. However, it is a known fact that young patients categorized into advanced functional classes are still capable of walking long distances and that the distance covered is also subject to the motivation of each patient at any given time. Furthermore, a meta-analysis performed on 22 randomized studies including a

total population of 3112 patients demonstrated that greater distances covered in the 6MWT were not a clear reflection of the clinical results obtained by the patients.¹¹

However, the CPET is a less accessible test, as it is not available in all centers, although it has been implemented in more PAH units in recent years due to its great usefulness in both the diagnosis and prognosis. Although this test requires more time and greater experience and training on the part of the personnel who perform it and the doctor who evaluates its results, it provides valuable cardiorespiratory data, information on the patients' objective functional class, and allows for determining the pathophysiological mechanisms that limit the exercise capacity.

In the last few years, multiple studies have demonstrated the usefulness of the CPET in the assessment of

patients with PAH. Nevertheless, VO_2 is a parameter that has been reported as an independent predictor of mortality in almost all relevant studies. In addition, other variables, such as those assessing ventilatory efficiency, have proven to be of particular relevance in the diagnosis and prognosis of PAH. Accordingly, in a study performed with patients with confirmed PAH, Yasunobu et al. described how ventilatory efficiency variables (end-tidal partial carbon dioxide pressure [$P_{et}CO_2$] and equivalent for carbon dioxide [$EqCO_2$]) had a good correlation with the mean pulmonary artery pressure (mPAP), whether at rest, at the anaerobic threshold, and at the maximum effort, and, therefore, by using these measures of ventilatory efficiency they were able to differentiate patients according to the degree of severity of their PAH.¹²

A study performed by Groepenhof et al., in which 115 patients with PAH were analyzed, demonstrated that ventilatory efficiency variables, in addition to the O_2 pulse and VO_2 measured during a CPET, had greater statistical power to predict mortality events than the hemodynamic variables included in their analysis (pulmonary vascular resistance [PVR], right atrial pressure, cardiac index, and mPAP). In fact, the change in the O_2 pulse between a state of rest and that of maximum effort was the variable exhibiting the greatest ability to predict mortality events.¹³

Another study performed on a population of 72 patients with PAH showed that certain CPET variables, such as the VO_2 , the ventilatory efficiency variables, and the O_2 pulse had the best statistical power to predict mortality events, once again superior to that of the hemodynamic variables.¹⁴

The O_2 pulse variable, which is calculated by dividing the VO_2 by the heart rate, is a particularly important measure in PAH, given that, in situations of maximum effort, it can be an indirect measure of the ventricular systolic volume through the Fick equation. In addition to the studies cited above, other studies have also demonstrated that ventilatory efficiency variables, the VO_2 , and the O_2 pulse have prognostic usefulness, including the one designed by Tang et al. to evaluate the usefulness of the CPET in the prognostic assessment of PAH.¹⁵

Recently, CPET has also been used, with stroke volume index, to better identify patients at intermediate risk, although only peak VO_2 expressed in absolute value was the variable included in this assessment.¹⁶

Hence, all of the above prove the usefulness of the CPET in the prognosis of PAH. However, there is currently no consensus on which cut-off points should be used for each parameter to establish the likelihood of PH. An additional difficulty is that there is no consensus either on the appropriate moment to measure the

ventilatory efficiency parameters (anaerobic threshold vs. point of maximum efficiency vs. maximum effort).

To date, we are unaware of the existence of other studies that have evaluated the concordance between the exercise tests proposed by the 2015 and 2022 ERS/ESC guidelines for PH and their concordance with other variables. Although we are very aware that the CPET is a crucial test in the diagnosis and prognosis of PAH, the results of our study highlight the importance of selecting appropriate cut-off points for each variable. On the one hand, it seems that there could be a good concordance between the 6MWT and the WHO functional class. However, there is a low concordance between the two proposed exercise tests, as the results of our study suggest that the 6MWT tends to underestimate the risk (no patients were classified as high-risk, whereas 72.9% were classified as low-risk), while the CPET variables tend to be more widely distributed among the three risk groups.

We also found a remarkable lack of concordance in the risk stratification determined using the different variables of the CPET itself, as 75% of the patients were categorized into different risk groups with this same test depending on the parameters used. It is true that the different parameters evaluate different aspects of the response to exercise: 6MWT evaluates aerobic capacity, VO_2 maximal effort capacity (aerobic and anaerobic), and VE/VCO_2 ventilatory efficiency. However, even more strikingly, 40.7% of these patients were classified into different risk groups when using the same variable; that is, VO_2 , depending on whether it was expressed in absolute units (ml/kg/min) or as a percentage related to the theoretical value. It is difficult to understand how the same variable classified patients into different risk groups almost half of the time depending on whether it was expressed as an absolute value or a percentage. To reduce inter-test variability between different sites, perhaps the next recommendations should include what reference values should be used to calculate the theoretical value of VO_2 .

Our study also had some limitations. On the one hand, it is a retrospective study that included data provided by only one center. Because younger patients have more skills than older patients to do complex exercise tests such as CPET, the mean age of our patients may be lower than that is described in some registries. Moreover, it suffers from a selection bias considering that our study population included patients who had completed a CPET and, given that in our institution we do not perform CPET in patients in functional class IV, it featured a low percentage of patients categorized into this functional class. In addition, the 6MWT and the CPET were not performed within the same time frame, which would have been the ideal situation to determine

this concordance. Nonetheless, only a median of 84 days elapsed between the conduct of both tests, and only 70 days between CPET and right heart catheterization, which is a reasonably short time that would allow for drawing conclusions.

To conclude, the results of our study demonstrate a significant discrepancy between the different risk assessment variables and that the same variables used in the same test, such as the CPET, can classify patients into different risk groups, even when a single variable is expressed in different units of measure. Therefore, the results of our study should be a call for reflection on whether or not the cut-off points set for the exercise tests proposed for the current risk assessment are adequate to achieve a correct risk stratification or whether they require an appropriate revision and re-editing, or even the use of other cut-off points, so as to include other simple measures such as the O₂ pulse, which has demonstrated its prognostic usefulness, or the need to modify the weight assigned to the different variables.

AUTHOR CONTRIBUTIONS

Conceptualization: Víctor M. Mora Cuesta and Amaya Martínez Meñaca. *Methodology:* Víctor M. Mora Cuesta; *Formal analysis:* Víctor M. Mora Cuesta. *Investigation:* Daniel Fernández Márquez, Begoña Sáinz-Ezquerria Belmonte and María José Gallardo Ruiz; *Writing – original draft preparation:* Víctor M. Mora Cuesta. *Writing – review and editing:* Amaya Martínez Meñaca, David Iturbe Fernández, Sandra Tello Mena, José M. Cifrián Martínez. *Supervision:* José M. Cifrián Martínez; *Project administration:* Pilar Alonso Lecue. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

This study protocol was reviewed and approved by Comité de Ética y Medicamentos de Cantabria, approval number [2020.009]. Informed consent was obtained from all subjects involved in the study.

ORCID

Victor M. Mora Cuesta  <http://orcid.org/0000-0002-8161-0462>

Amaya Martínez Meñaca  <https://orcid.org/0000-0003-4141-8887>

David Iturbe Fernández  <https://orcid.org/0000-0002-5241-266X>

Pilar Alonso Lecue  <https://orcid.org/0000-0002-8696-3435>

José Manuel Cifrián Martínez  <https://orcid.org/0000-0003-3682-0142>

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