The Value of Exercise Testing in the Diagnosis of Pulmonary Arterial Hypertension

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ABSTRACT
Exercise capacity impairment and dyspnea are the most frequent clinical signs showed by patients affected by pulmonary arterial hypertension (PAH). Consequently, a patient with these symptoms should be investigated to confirm or rule out this diagnosis. A functional evaluation, done by six-minute walking test and/or cardiopulmonary exercise test, can help physicians to clarify diagnosis, potential treatment and prognosis.

In this review Authors deal with delicates mechanisms underlying exercise physiopathology of PAH and interpretation of tests currently used to investigate exercise limitation in these patients. (Tur Toraks Der 2008;9:167-73)

Key words: Dyspnea, exercise, 6 minute walking test, cardiopulmonary exercise test, pulmonary arterial hypertension

INTRODUCTION
Pulmonary arterial hypertension (PAH) is a rare but severe disease with a poor prognosis, that means, in its untreated form, a median life expectancy of 2.8 years from the time of diagnosis [1]. The disease is characterized by a pulmonary vasculopathy that progressively increases the pulmonary vascular resistance, leading to premature death due to right ventricular failure.

The prominent symptoms are usually related to exertion, with 90% of patients presenting with excessive dyspnea [2]. Syncope, chest pain, weakness, peripheral oedema and abdominal distension, are also common in these patients but all of these symptoms are non-specific. (Table 1)

Moreover, the evaluation of dyspnea aetiology is frequently a challenge for clinicians; the consequence is that the disease is often misdiagnosed and wrongly treated for other more common conditions with a consequent delay between symptoms onset and the appropriate treatment.

As reported in Clinical Guidelines, the evaluation of exercise performance, using six minute walking distance and/or cardiopulmonary test (CPET), is an important step in the diagnostic course, in PAH staging and in the subsequent clinical follow up [3].

<table>
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<th>Table 1. Main symptoms and their frequency in PAH patients</th>
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<tr>
<td>Dyspnea</td>
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<td>Fatigue</td>
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<td>Peripheral edema</td>
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<td>Sincope</td>
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<td>Light-headedness</td>
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<td>Chest pain</td>
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<td>Palpitations</td>
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PAH patients present at CPET with reduction in oxygen uptake at peak exercise and at anaerobic threshold, in oxygen pulse, ventilatory efficiency at CPET and at 6 minute walking test (6MWT) present with reduction in walking distance. All these parameters are correlated with functional class and survival even more than resting pulmonary hemodynamic measurements.

In this review the pathophysiology of dyspnea and exercise tolerance in pulmonary arterial hypertension and the key role of exercise tests in the diagnosis, follow up and prognosis of PAH patients are reported.

**PATHOPHYSIOLOGY OF EXERCISE INTOLERANCE IN PAH**

I) **Arterial blood gases.** It is well known that PAH is commonly associated with abnormal arterial blood gases, with mild-to-moderate hypoxemia and mild-to-moderate hypocapnia, as expression of increased intra-pulmonary shunt, of the impairment in alveolar capillary oxygen diffusion and oxygen delivery and of the consequent hyperventilation present already at rest. However, neither levels of oxygen arterial partial pressure (Pao₂) nor values of carbon dioxide arterial partial pressure (Paco₂) correlate with hemodynamic parameters [4].

II) **Lung function.** A mild restrictive lung function pattern, with a minor reduction in total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), maximal voluntary ventilation (MVV) and alveolar volume (VA), has been frequently observed. However the restrictive lung disease is unlikely the explanation for the severe exercise dyspnea observed in PAH patients. Furthermore airways obstruction is uncommon in patients affected by PAH. Interestingly, albeit a low MVV, at peak exercise, PAH patients generally fail to exhaust their breathing reserve as it is demonstrated by the difference between peak exercise ventilation and MVV, indicating that the decreased ventilatory capacity doesn’t appear to limit the maximal exercise capacity. There is no significant correlation between resting lung function parameters and resting hemodynamic values obtained at right heart catheterization nor with functional class. It has been hypothesised that in these patients lung restriction may be due to both cardiomegaly, with right ventricular hypertrophy and dilatation, and to the decrease of small arteries normal distensibility that limits lung expansion and reduces its compliance [5].

III) **Carbon monoxide diffusion capacity.** In PAH patients a moderate loss of carbon monoxide diffusion capacity (DLCO) has been demonstrated. The reduction of DLCO seems to be primarily caused by a decrease in membrane component of DLCO (DM) and, to a lesser extent, by a decrease in capillary volume (Vc). This may results from the development of plexiform lesions, the typical hystopathological finding in PAH, which lead to obstruction and obliteration of arterioles by exuberant muscular cell growth of the media, and from the monoclonal proliferation of endothelial cells leading to alveolo-capillary membrane thickening. In a study involving idioopathic and post-tromboembolic pulmonary hyperten-

sion patients, DM has been showed strongly related to pulmonary vasculature resistance. The strong relation between DLCO and several cardiopulmonary parameters confirms that the primary exercise limiting process is not ventilation but involves blood vessel of the lung [6]. In fact exercise limitation in patients with PAH cannot only be explained by inefficient lung gas exchange but mainly by reduced oxygen delivery, which is the product of cardiac output and arterial oxygen content, both reduced in PAH patients at peak exercise.

IV) **Cardiac output.** In PAH patients cardiac output can be normal at rest but it fails to increase enough to fill the peripheral tissue oxygen demand during exercise. This was demonstrated in a study by Holverda et al. [7], where cardiac function was assessed by MRI both at rest and during submaximal exercise in 10 PAH patients and 10 matched control subjects: PAH patients reached a lower exercise workload because they were not able to significantly increase their stroke volume from rest to exercise, as compared with healthy subjects. The proposed explanation was an impaired underfilling of the left ventricle which is in turn caused by a reduction of both “vis a fronte” and “vis a tergo”: the first is explained by an increased in right ventricular end-diastolic volume which induces opposite changes in the other ventricle according to the ventricular-interdependence mediated by both pericardium and ventricular septum; the second is explained by a reduced right ventricle stroke volume related to an excessive exercise-induced rise in pulmonary arterial vascular resistances.

In another study, Deboeck at al. [8] showed that PAH patients have, during exercise, a severely reduced peak O₂ pulse, as expression of stroke volume. Moreover Nootens at al. [9] observed not only a missing increase, but also a decrease in stroke volume near to maximal exercise. The inadequate cardiac output response to exercise results in an increase in anaerobic glycolysis, with development of lactic acidosis and the consequent increase of CO₂ production (VCO₂), also at low work rates.

V) **Ventilation/Perfusion match.** VCO₂, arterial CO₂ tension (PaCO₂) and the ratio between dead space ventilation and tidal volume (VD/Vt) are the three physiological factors involved in the ventilatory response to exercise and all are implicated into the mechanisms which lead to premature onset of dyspnea and the low exercise tolerance in PAH patients; in particular the magnitude of the ventilatory response is directly related to the CO₂ production and VD/Vt and inversely related to the PaCO₂ [10]. Indeed, in normal subjects, VD/Vt decreases during exercise, making a more efficient ventilation / perfusion match, while, in PAH patients, VD/Vt increase, due to reduced perfusion to ventilation match in lungs (Figure 1).

Minute ventilation (VE) is higher in PAH patients for any level of VCO₂ as compared both in healthy subjects than in heart failure patients; this could be mediated by chemo-receptor control mechanism, as in heart failure patients, and also by non-chemo-receptor control mechanisms; indeed hypoxemia is usually lower than normally required for significant stimulation of hypoxic chemoreceptors.
As showed by Yasonobu et al. [11], the rise in VD/Vt, results in exercise-induced arterial haemoglobin desaturation and reduction in end-tidal pressure of CO₂ (PetCO₂). These authors also found that both these parameters well correlate with the disease severity. However, Schwaiblmair et al. [12], in a study considering a group of patient with systemic sclerosis, suggested a role of the increased VD/Vt in exercise intolerance and found a trend between the reduction in DLCO and the increase in VD/Vt as well as the widening in the alveolar-arterial oxygen gradient (P(A-a)O₂), as expression of the pulmonary vasculitic damage of systemic sclerosis.

VI) Respiratory muscle. Kabitz et al. [13] proposed that also an impairment of respiratory muscle function might contribute to dyspnea and exercise intolerance in PAH patients as it was demonstrated in heart failure patients [14]. The causes of the reduced respiratory muscle strength aren’t known but these authors suggested a role for a depressed oxidative capacity of the working muscles linked to under-perfusion and deoxygenation of respiratory muscles during exercise; even hyperventilation itself enhanced the demands on inspiratory muscles. Finally, as pointed out by Tolleed at al. [15], also maximum systemic oxygen extraction may be impaired in pulmonary arterial hypertension and contributes to exercise limitation.

THE SIX MINUTE WALKING TEST

The simplest assessment of exercise capacity in PAH is the World Health Organization (WHO) functional classification which is an adaptation of the NYHA classification used in heart failure patients, modified with the reference to PAH-related symptoms [16]. Despite this classification has been shown to correlate with disease severity and outcome, its major limitation is that it depends upon patients reporting their own symptoms [1,17]. So, patients who over- or under-estimate their physical limitations can lead the clinicians to make incorrect conclusions about their disease severity. In addition, despite widely accepted definitions, great variability exists in how physicians assign functional class.

Therefore, the Guidelines of the European Society of Cardiology recommend an objective assessment of exercise capacity in PAH patients, using the six minute walking test (6MWT) and/or CPET, which should be performed at the time of diagnosis, to establish baseline functional impairment, and during the follow-up to assess response to therapy and prognosis [3].

The 6MWT is a sub maximal exercise which gives a good indication of the ability to perform daily life activities, providing a simple and comprehensive evaluation of the cardiovascular, respiratory and muscular response to exercise. The primary measurement is the distance walked in 6 minutes; however also blood oxygen saturation, collected by a portable oximeter, and patient’s perception of dyspnea and fatigue according to Borg scale needs to be added (Table 2). Recently, the American Thoracic Society guidelines provided a standardized approach for performing the test [18]. The 6MWT is easy to perform, inexpensive, highly reproducible, safe and good tolerated also in advanced functional class patients because they tend to self-limit their walk rate, while a maximal stress test may be difficult to perform in these subjects. For these advantages several clinical trials used the 6MWT to assess functional capacity improvement of PAH patient, in response to therapy [17, 19,23]; unfortunately only few studies consider the clinical meaning of 6MWT. For instance, Miyamoto at al. [24] demonstrated in 43 PAH patients, that the distance walked during the 6MWT significantly decreased in proportion to the severity of NYHA/WHO functional class. Moreover in this study, the patients were divided into two groups, labelled “short distance group” and “long distance group” according to the median value of the distance walked in 6 minutes, respectively <332 mt. and ≥332 mt.; statistically significant differences were found between the two groups in cardiac output, total vascular resistance and right atrial pressure, while no difference were found in the other hemodynamic variables nor in demographic parameters. Therefore the 6MWT distance resulted directly related to peak VO₂ and oxygen pulse, determined by maximal cardiopulmonary test. These results suggested that the distance walked may be related to maximal exercise capacity determined by CPET and that a short distance walked during the 6MWT reflects an insufficient oxygen delivery during exercise.

Table 2. Borg Scale for dispnea and fatigue feeling

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>NOTHING AT ALL</td>
</tr>
<tr>
<td>1</td>
<td>VERY LIGHT</td>
</tr>
<tr>
<td>2</td>
<td>FAIRLY LIGHT</td>
</tr>
<tr>
<td>3</td>
<td>MODERATE</td>
</tr>
<tr>
<td>4</td>
<td>SOME WHAT HARD</td>
</tr>
<tr>
<td>5</td>
<td>HARD</td>
</tr>
<tr>
<td>6</td>
<td>…</td>
</tr>
<tr>
<td>7</td>
<td>VERY HARD</td>
</tr>
<tr>
<td>8</td>
<td>…</td>
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<tr>
<td>9</td>
<td>…</td>
</tr>
<tr>
<td>10</td>
<td>VERY, VERY HARD</td>
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Differently, in the STRIDE-1 study a correlation between 6MWT and CPET measurement was not found. Indeed, with the treatment, an improvement in 6MWT both at six and 12 weeks was observed without significantly changes in CPET parameters; however, Oudiz et al. [25] demonstrated that when the 6MWT distance was adjusted for each patient’s weight the correlation between the weight-adjusted 6MWT distance and peak VO₂ markedly improved. In fact the 6MWT distance, in opposite to the CPET, does not consider the metabolic cost of the exercise, so two subjects can have identical 6MWT distance values but different functional capacity if they have a markedly different body weight.

The 6MWT distance is not only a numeric expression of patients’ functional ability but also a powerful prognostic indicator which well correlate with survival. Indeed, in the study of Miyamoto at al. [24], the 6MWT distance resulted, at the multivariate analysis, the only independent predictor of mortality and the Kaplan-Meier survival curves drawn according to the median value of distance walked, demonstrated that patients walking <332 mt. had a significantly lower survival rate than those walking more. This trend was confirmed by Sitbon et al. [17]; however these authors also proved that the increase in 6MWT distance from baseline to three months of epoprostenol, did not correlate with survival.

Paciocco et al. [26] demonstrated that, in a group of moderately symptomatic patients with PAH, the O₂ saturation at the end of exercise and the difference between rest and exercise O₂ saturation (ΔSatO₂), were both independent predictors of mortality; in particular they found that the mortality risk is increased 2.4 fold in patients who are able to walk less than 300 mt. in 6 minutes and 2.9-fold in those with >10% decline in arterial oxygen saturation during the 6MWT [25].

The 6MWT has been the most common measure of exercise capacity and it is often used as primary end point in multicenter clinical trials in PAH, but in addition it is easier and cheaper to administer than CPET and doesn’t require technical training for laboratory personnel. It has not been validated as an end point in PAH patients with less severe disease; unfortunately the 6MWT is more influenced by test familiarity and motivation than CPET [26].

Measurement of ventilation and pulmonary gas exchange during exercise testing provides additional information about physiologic abnormalities associated with the underperfusion of the pulmonary vascular bed seen in PAH.

A functional interdependence between muscle activity, circulation and lungs, exists and it is directed to couple the cellular and the pulmonary respiration; thus, the O₂ utilization by the muscles depends first, on an adequate ventilation and lung gas exchange, second on a sufficient increase in cardiac output and in pulmonary blood flow, and finally on the amount of O₂ extraction from the blood perfusing the muscles themselves [28].

Heart failure patients also exhibit exercise intolerance, which may be due to an anomaly in any of the three components above mentioned, eventually one prevailing on the others. However, in PAH patients, the exercise ability is mainly compromised by a failure in lung gas exchange and by an inadequate stroke volume increase during exercise due both to a deficient exercise-induced vasodilatation of existing lung vessels and a lacking recruitment of new ones, both to the consequent right ventricle failure.

I. Analysis of VO₂

The CPET discloses PAH exercise patophysiology in the reduction of workload, peak VO₂ (pVO₂), anaerobic threshold (AT), O₂ pulse and PETCO₂ and in a steeper slope of VE/VCO₂.

pVO₂ assesses the exercise capacity and represents the ability of CO and oxygen peripheral extraction to increase as requested by muscles during exercise. Several studies reported a pVO₂ in PAH patients significantly reduced in comparison with healthy subjects, equal to about 40% of normal control and lower also than heart failure patients with an equivalent NYHA class [2,29-32].

In PAH patients, the reduced O₂ delivery leads to a O₂ end-capillary pressure drop down, thus the metabolism prematurely switches to a glycolitic adenosine triphosphate production and AT results markedly anticipated, developing an acidosis at low work rate, which, in turn, overproduces the fatigue feeling and the acid ventilatory drive.

The positive correlation showed by D’Alonzo et al. [29] between AT and pulse O₂ demonstrates that, during exercise, the impaired peripheral O₂ delivery, as reflected by an early developing of AT, is related to an inadequate increase in stroke volume, as expressed by low maximal O₂ pulse values. Moreover the authors suggested that this limit may be partially in counter balanced by an increase in heart rate (HR), as demonstrated by lower O₂ pulse values and higher HR in the PAH group than in control subjects, at all levels of oxygen consumption. Therefore an abnormally low rate of VO₂ rise in response to increasing work rate (WR), is expression of an insufficient O₂ delivery during exercise.

In healthy subjects the slope of the VO₂/WR relationship is around 10 ml/min/W; in contrast, in a study of
Riley et al. [30] a reduction in the VO₂/WR slope in PAH patients above the AT was found. The VO₂/WR slope decrease was significantly greater than that reported for patients with coronary heart disease and for heart failure, suggesting a very severe circulatory impairment in PAH patients.

The compromised O₂ transport from the atmosphere to the mitochondria may, at least initially, be sustained by optimizing the peripheral O₂ extraction, which is also facilitated by acidemia-induced O₂ unloading from haemoglobin. However, the unproductive association between the anticipated acidosis and the limited compensatory reserve capacity of HR and O₂ extraction increasing, leads to an exercise exhaustion at low workload, because of premature dyspnea and fatigue onset (figure 2).

II. Ventilatory parameters

Despite the common complaint of dyspnea, no evidence of ventilatory limitation has been reported in the studies including PAH patients performing CPET [2,29-32]. The VE found in PAH patients by D’Alonzo et al. [29] was similar to that in control subjects, neither group exceeding the 60% of the predicted VE. However, VE was higher at any level of VCO₂ in PAH group than in normal group, both at rest and during exercise [28]. Riely et al. [30] confirmed a greater increase in the ventilatory equivalent for VO₂ (VE/VO₂) and for VCO₂ (VE/VCO₂) in PAH patients than in healthy subjects, indicating inefficiency in gas exchange and altered ventilation/perfusion match [29]. In normal subjects, VE response to exercise above AT is tightly proportional to VCO₂ increase, due to CO₂ generation by the bicarbonate buffering of lactic acid in addition to the metabolic CO₂ production. This phase is labelled the “isocapnic buffering”, characterized by PaCO₂ and PetCO₂ remaining stable. In contrast, in PAH patients, the rise in dead space ventilation manifests with an hyperbolic increase of VE relative to VCO₂, with isocapnic buffering disappearing. The consequent important increasing in VE/VCO₂ slope has been considered an expression of a pulmonary vascular limitation to exercise [33]. Yasonobu et al. [11] demonstrated a lower rest PetCO₂ in PAH patients than in normal subjects, with an abnormal pattern of P₄₀/CO₂ in response to exercise and during the recovery. P₄₀/CO₂ is the end-tidal CO₂ pressure measured at the patient’s mouth and, in healthy subjects, it typically increases from rest to AT, it remains stable or slightly reduces during the isocapnic buffering and then it visibly decreases in the ventilatory compensation phase, where the lactic acidosis, no longer buffered by bicarbonate, enhances the acid ventilatory drive. In contrast in PAH patients, P₄₀/CO₂ is reduced at rest and it continues to further decrease during all exercise because of excessive hyperventilation, this except for PAH patients with mild disease, whose reduced resting P₄₀/CO₂ remained unchanged until AT. The same authors also demonstrated that the degree of the P₄₀/CO₂ decrease between rest and AT was greater as the percentage of predicted AT reduced.

III. Desaturation

P₄₀/CO₂ reduction and equivalents respiratory increase were found to correlate with O₂ desaturation during exercise. Therefore this abnormality has been attributed not only to the impairment in the alveolo-capillary membrane diffusing capacity and to the reduction in mixed venous blood O₂ saturation due to an enhanced O₂ peripheral extraction, but overall to the presence of pulmonary shunts, both functional (hyperventilation of poorly perfused alveoli) and anatomic (opening of veno-arterial shunts). The most marked anomalies of O₂ saturation, P₄₀/CO₂ and VE/VCO₂ have been demonstrated in PAH patients with a atrial septal defect and right-to-left shunt [33].

In figure 3 is reported a CPET explanatory example of a 35 years old female patient affected by primary PAH with a severely compromised hemodynamic pattern II functional class and a 6MWT distance of about 600 mt. A brief clinical comment of this CPET graphs and results
will follow.

Although the low workload achieved, the exercise resulted maximal as revealed by a respiratory ratio exchange value >1.1. Despite the long distance walked during 6MWT, pVO2 reached by the patient, reveals a severe reduction in exercise capacity, equal about to the 40% of predicted value with a significantly anticipated AT; particularly the V-slope plot showed a markedly steep slope of the relation VCO2 / VO2 above AT, expressing the faster rate of lactate production relative to the VO2 increase. The main exercise limitation was cardiogenic as revealed by the low O2 pulse and reduced slope of the VO2/WR relationship with a typical VO2 flattening above AT. As expected, no ventilatory limitation was demonstrated, being VE less than 60% of the predicted value. Also behaviour of ventilatory parameters, VT and RR, was quite normal, except for an high value of VT at rest that quickly reached a plateau. The non-invasive indicators of ventilatory efficiency, VE/VCO2 and PTECO2, resulted significantly altered, increased and reduced respectively, both at rest and during exercise expressing a vascular pulmonary limitation. Gas exchange impairment was confirmed by a markedly O2 desaturation during exercise.

Beside the supplied substantial physiologic information, CPET has the potential of noninvasively grading the disease severity and assessing responses to therapy, providing also important prognostic tools. Sun et al. [2] graded 53 patients in 4 classes of PAH impairment according to the severity reduction in CPET aerobic capacity (% of the predicted VO2), named mild, moderate, severe and very severe respectively. It is well known that CPET ventilatory parameters are related to both NYHA class and resting pulmonary hemodynamics. However, the absence of overlap in any parameters of aerobic function (pVO2, AT, peak O2 pulse, VO2/work) or VE/VCO2 between the 4 PAH classes and between normal subjects compared to PAH patients of mildest severity, suggested a better discriminating power of CPET than the functional class and the main rest hemodynamic parameters.

Yasunobu et al. [11] confirmed the good correlation between percentage of predicted max VO2 and VE/VCO2 to hemodynamic mean pulmonary artery pressure, but this parameter resulted better related to PTECO2 values, not only at peak exercise but also at AT and at rest, with an inversely proportional relationship. Particularly PTECO2 values got progressively lower as disease severity increased, with an opposite change compared to normal subjects; there was also a significant difference between PAH classes in the O2 saturation drop at peak exercise, while rest pO2 values were almost equal in all groups. Indeed in a subsequent study about the prognostic meaning of emogasanalysis in PAH, only CO2 arterial pressure at rest resulted an independent marker of mortality, reflecting the increased ventilatory drive [4].

IV. Prognosis

In a group of 86 PAH patients Wensel et al. [32] demonstrated that pVO2 >10.4 ml/Kg/min and blood systolic pressure at peak exercise >120 mmHg were the only independent and highly accurate predictors of survival in the multivariable analysis, while hemodynamic parameters resulted predictive of survival just at univariate analysis. Also VE/VCO2 slope resulted significant predictor of mortality at univariate analysis, but it was removed from the multivariate analysis because it would have limited the analysis to the patients without a PFO, that represented almost the 35% of the study population.

Recently Galie et al. [35] demonstrated survival improvement by treatment with bosentan, even in PAH patients with mild functional class, suggesting the prognostic utility of an early diagnosis. Therefore the importance of an early diagnosis calls for an extensive evaluation of subjects with an high risk to develop PAH, such those affected by systemic sclerosis. With this purpose, Reaside et al. [36] evaluated 10 patients with suspected PAH showing a statistically significant relationship between ventilatory equivalents and mean pulmonary artery pressure, measures with a micro-manometer tipped pulmonary artery catheter during CPET. Moreover a hyperbolic relation between PTECO2 and VE/VCO2 at AT was found by Yasunobu et al [11] and it was connected to the likelihood of PAH accounting for exertional dyspnea of unknown causes.

Consequently CPET parameters could be used as non-invasive surrogate markers of vasoreactive response of pulmonary circulation.

CONCLUSIONS

The understanding and diagnosis of a such complex disease, requires an extensive comprehension of PAH different physiopatological mechanisms, pursuing a detective-like method which should pass through a series of progressively more complex assessing parameters.

At present CPET is the most complete instrument we have to understand and interpret the heart-lung-muscle machine failure and the consequent impairment in exercise production. CPET more extensive use will allow a better understanding of disease physiology, will help treatment and overall will produce a better patient care.

REFERENCES