

## Lack of Tight Association Between Quality of Life and Exercise Capacity in Pulmonary Arterial Hypertension

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### Abstract

**Background:** In pulmonary arterial hypertension (PAH) health-related quality of life (HRQOL) has been investigated over the short-term (weeks) but little is known about patient's perspective over the medium and long term.

**Objective:** To analyze how patients on specific PAH therapies do over one year of observation in terms of HRQOL, and to investigate if possible associations between the exercise capacity (EC) and HRQOL persist over the medium term.

**Methods:** Thirty-four patients on PAH therapies (bosentan and/or sildenafil) were enrolled (age 14 to 58 years, median 35.5 years, functional class II or III), and evaluated at baseline, and 3, 6, 9 and 12 months subsequently using the six-minute walk test and the SF-36 HRQOL questionnaire.

**Results:** The six minute walked distance did not change over the follow-up (387-432 meters, median values,  $p=0.2775$ ), the same for the functional class and peripheral oxygen saturation. The SF-36 scores also remained stable, with physical health always worse than mental health. Of 40 possible associations between EC and HRQOL, only 12 were significant (30%,  $p<0.05$ ). Prediction of severely depressed HRQOL based on a walked distance of  $<235$  meters was  $>90\%$  specific but  $<43\%$  sensitive.

**Conclusion:** Patients with PAH who remain stable in terms of EC also seem to do so in terms of HRQOL. However, EC and HRQOL are not consistently tied over time, and should be analyzed as different perspectives in the individual patient. (Arq Bras Cardiol 2012;99(4):876-885)

**Keywords:** Pulmonary hypertension; quality of life; exercise tolerance; symptoms.

### Introduction

Pulmonary arterial hypertension (PAH) is a devastating disorder characterized by elevation of pulmonary artery pressure and vascular resistance, progressive dyspnea and exercise limitation and ultimately, right cardiac failure and premature death. Fortunately, in the last decades, there has been considerable progress in terms of awareness, early diagnosis and specific pharmacological interventions<sup>1-7</sup>. The effects of such interventions have been analyzed taking into consideration the physical capacity (generally assessed by the six-minute walk test)<sup>8</sup>, time to clinical worsening, hemodynamics and survival.

There has been growing interest on the analysis of health-related quality of life (HRQOL) in this disorder. The diagnosis of PAH and the clinical perspectives impose a considerable burden on patients and families in terms of prognosis and treatment-related difficulties. In this way, HRQOL has been included as an additional end-point in clinical studies aimed

at investigating the potential benefits of new PAH therapies. Improvement of HRQOL has been reported in patients on these therapies, but not consistently in all studies or when different questionnaires are used in the same study<sup>3,9-12</sup>. In addition, correlations have been demonstrated between HRQOL and exercise capacity, but not hemodynamics<sup>13-15</sup>. Thus, despite initial progress, the study of HRQOL in PAH remains a nascent field relative to other diseases.

In many instances, HRQOL has been assessed over weeks of treatment to investigate the impact of new PAH therapies in comparison with the pre-treatment status. The literature is scarce in terms of examining HRQOL over months or years in patients on treatment. Furthermore, because the correlations between the exercise capacity and HRQOL are relatively weak and have been investigated in cross-sectional studies, it is not possible to know if they remain significant over time. We therefore decided to examine HRQOL in PAH patients who were already on chronic specific therapies. The study was aimed at investigating how patients do in terms of HRQOL over 12 months of follow-up. We also wondered if associations between the exercise capacity and HRQOL remain stable over time. Using appropriate statistical models, we specifically investigated if it was possible to predict patient's quality of life on the basis of the physical capacity as assessed by the Six-minute walk distance.

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## Methods

### Patients

Adolescents and adults with PAH assisted as outpatients were consecutively enrolled. Idiopathic PAH and PAH associated with congenital heart disease were the only diagnostic categories in the study. The last category included individuals with moderate disease (acyanotic, peripheral oxygen saturation of  $\geq 90\%$ ) and subjects with more advanced disease, with typical presentation of Eisenmenger syndrome (cyanotic, peripheral oxygen saturation of  $< 90\%$ ). All patients in the study were considered as unsuitable for surgical correction of the cardiac anomaly due to moderate to severe pulmonary vascular disease, and were under treatment with drugs approved for PAH. Only patients under ambulatory care were enrolled. All subjects were in stable functional class II or III (World Health Association classification for PAH) when they entered the study. For inclusion, a written informed consent was required.

### Parameters and follow-up

The diagnosis of idiopathic PAH or PAH associated with congenital heart disease was established on the basis of previously approved diagnostic protocol<sup>16,17</sup>. Doppler-echocardiography was used to characterize the congenital cardiac anomaly when present, and to estimate the pulmonary arterial systolic pressure in all patients. After initial evaluation, patients were seen at three, six, nine and twelve months. In all those instances, the functional status and the quality of life were evaluated by distinct observers.

The functional class was registered according to the classification of the New York Heart Association modified for pulmonary hypertension by the World Health Organization. The exercise capacity was determined by measuring the Six-minute walk distance according to the protocol (six-minute walk test) approved by the American Thoracic Society<sup>8</sup>. Peripheral oxygen saturation was measured by pulse oxymetry at rest and at the end of the six-minute walk.

The quality of life was analyzed using the SF-36 generic questionnaire (The Medical Outcomes Study 36-item Short-Form Health Survey)<sup>18</sup>. After an initial explanation, patients were asked to read and answer the questions themselves. No additional help was provided unless absolutely necessary. Final analysis was carried out, and a score was obtained for each category of the Physical Component (physical functioning, role physical, bodily pain and general health) and the Mental Component (vitality, social functioning, role emotional and mental health). Summary scores were also obtained for each of the two components.

### Statistical analysis

In view of the non-Gaussian distribution of most variables in the study, results are expressed as median value and range, and illustrated using box-plots. Differences between two independent groups (for example, diagnostic groups or functional class II versus III at baseline) were analyzed using the Mann-Whitney test. Differences between multiple correlated measures (over the follow-up) were tested using the

Friedman's statistics. Categorical variables were analyzed using the Chi-square statistics. Correlations between variables were tested by calculating the Spearman's coefficient of correlation ( $r_s$ ). In the particular case of testing the correlation between summary scores (Gaussian distribution accepted), the Pearson's coefficient was calculated. Logistic regression analysis was used to investigate if it was possible to predict the quality of life (specifically, a poor quality of life as indicated by SF-36 scores  $\leq 25$ ) based on the shortness of the distance walked during the six-minute test; receiver operator characteristic (ROC) curves were constructed accordingly. In all tests, 0.05 was assumed as significance level.

## Results

Thirty-four patients under specific PAH therapies were enrolled. At baseline, 30 patients were receiving oral sildenafil (20-80 mg t.i.d.), one patient was on oral bosentan (125 mg b.i.d.) and three patients were on combination therapy with both drugs. Demographic, diagnostic and functional data are depicted in Table 1. Despite the stable clinical condition (25 patients were in functional class II), the overall exercise capacity could not be considered as satisfactory, since the Six-minute walk distance (median 399 meters) was relatively short for a young patient population (median age 35.5 years). Patients with PAH associated with congenital heart disease had lower oxygen saturation as compared with those with idiopathic PAH ( $p=0.0136$  and  $p=0.0022$  respectively for differences at rest and during exercise).

Of the eight categories of the SF-36 questionnaire, median scores below 50 were observed in two, both related to physical health (Figure 1). A significant positive correlation was observed between the physical and mental components (Figure 2). Of all associations tested between HRQOL (physical and mental health summary scores) and clinical parameters (age, etiology of PAH, functional class, Six-minute walk distance and peripheral oxygen saturation), only the one between patient's functional class and physical health was significant. Patients in functional class II had a physical health summary score of 28.5 to 87.8 (median 57.8), while those in class III had a summary score of 18.0 to 60.5 (median 30.0) ( $p=0.0089$ ).

During 12 months of follow-up, two patients with Eisenmenger syndrome died (one of them on sildenafil 80 mg t.i.d. and the other one on sildenafil plus bosentan). The first patient was a 29-year old male, initially in functional class II. He completed four visits (baseline, three, six and nine months of follow-up). The mean values of the Six-minute walk distance, peripheral oxygen saturation (resting), physical health summary score and mental health summary score were 375 meters, 70%, 42.0 and 83.8, respectively. He had severe systemic hypertension associated with moderate to severe renal dysfunction. The second patient was a 55-year old female, initially in class III. She completed three visits only. The mean values of the mentioned parameters were 115 meters, 80%, 24.0 and 36.6, respectively. Another patient with initial diagnosis of Eisenmenger syndrome and receiving sildenafil was lost to follow-up. Thirty-one patients completed five visits (12 months of follow-up). Considering that six patients initially receiving sildenafil migrated to combination therapy,

**Table 1 – Baseline demographic, diagnostic and functional data in 34 pulmonary arterial hypertensive patients**

Age (years)	35.5 ( 14 – 58)	
Female : Male	24 : 10	
Etiology of PAH (N)		
IPAH	10	
HPAH	2	
PAH-CHD	22	
Functional class* (N)		
II	25	
III	9	
Heart rate (b.p.m.)	77 (57 – 98)	
Systemic pressure (mmHg)		
Systolic	110 (80 – 140)	
Diastolic	70 (50 – 90 )	
Pulmonary artery systolic pressure† (mmHg)	111 (43 – 155)	
Six-minute walk distance (meters)	399 (177 – 564)	
Peripheral oxygen saturation (%)	<b>Resting‡</b>	<b>Exercise‡</b>
IPAH	96 ( 83 – 98)	93 (74 – 98)
PAH-CHD	88 (63 – 98)	75 (38 – 97)

\* World Health Organization, adapted for pulmonary hypertension

† Estimated noninvasively by Doppler-echocardiography

‡  $p=0.0136$  and  $p=0.0022$  versus idiopathic PAH respectively at rest and at the end of the six-minute walk

PAH: pulmonary arterial hypertension

PAH-CHD: pulmonary arterial hypertension associated with congenital heart disease

IPAH: idiopathic pulmonary arterial hypertension

HPAH: hereditary pulmonary arterial hypertension

Results of numeric variables are presented as median value and range.

the final therapeutic scenario was as follows: 22 individuals on sildenafil, one on bosentan and eight on both drugs.

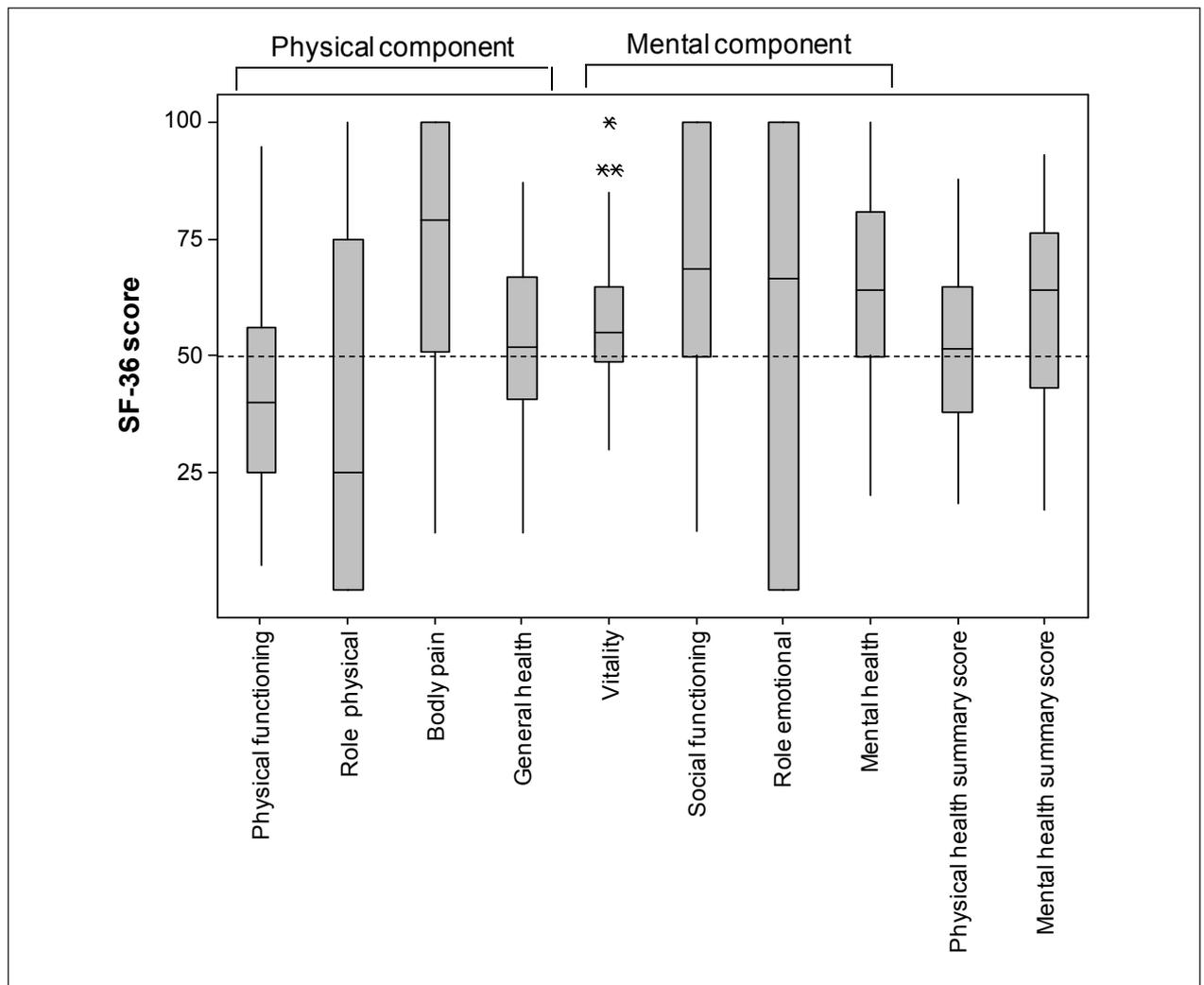
Functional data of 31 patients who completed the follow-up are depicted in Table 2. Essentially, there were no significant changes in the functional class, Six-minute walk distance and peripheral oxygen saturation (at rest and at the end of the six-minute walk). Regarding the quality of life, Figure 3 shows that physical and mental health, as assessed by the SF-36 questionnaire did not change significantly either. All over the follow-up, physical health tended to be a little worse when compared with mental health.

Possible associations were tested between the exercise capacity, as measured by the Six-minute walk distance, and each of the eight categories of the SF-36 questionnaire over 12 months of observation. Of the 40 possible associations that were investigated, 12 were significant, with positive correlations between the walked distance and the SF-36 scores (Table 3). In six of these 12 instances, it was possible to fit a logistic regression model to determine the lower limit of the Six-minute walk distance at which patients would very likely start to consider themselves as severely disabled (quality-of-life scores  $\leq 25$ ). Table 4 shows that such limit was somewhere between 235 and 280 meters, with high specificity. However,

the low sensitivity of prediction indicated that many patients would be unsatisfied about their quality of life even above this range. Finally, the receiver-operator-characteristic curves shown in Figure 4 indicate that the ability to predict the quality of life on the basis of the exercise capacity was quite variable depending on the parameter analyzed.

## Discussion

Quality of life has become a matter of progressive interest in a number of chronic diseases including chronic renal failure<sup>19-21</sup>, rheumatic disorders<sup>22,23</sup> and chronic failure<sup>24-26</sup>. In all these conditions, HRQOL has been assessed as an additional measure of the clinical status, as a measure of treatment effectiveness, and in association with indices of severity of the disease, morbidity and mortality. Conceptually, HRQOL represents a person's satisfaction in those areas of life likely to be affected by health status: physical capacity, cognitive ability, relationships, emotions and spirituality. It is therefore subjective, multidimensional and temporal<sup>27</sup>. In this way, methodological issues are raised of how to accurately assess HRQOL, and what might be the appropriate tools to test for possible associations with direct measures of disease severity and prognosis. Although the development of disease-specific HRQOL questionnaires



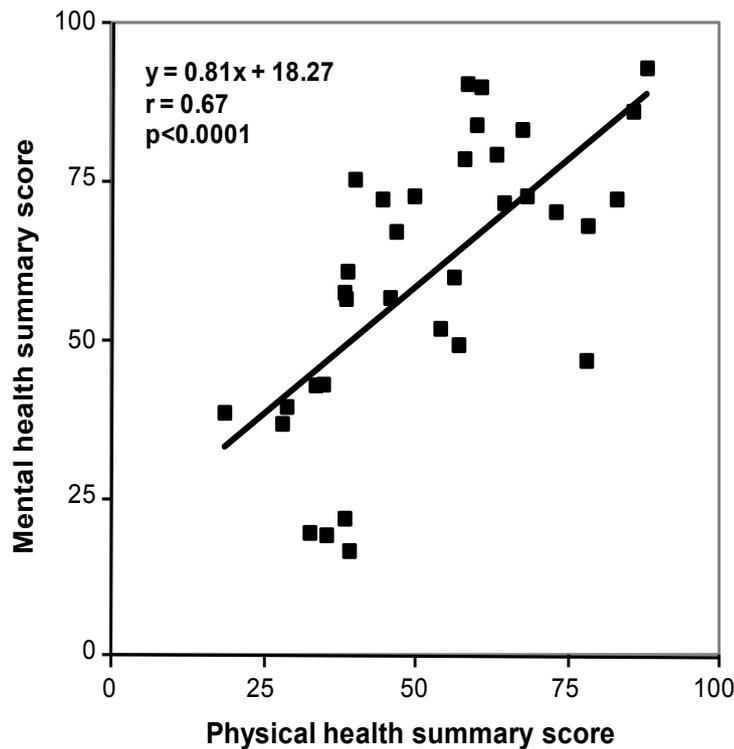
**Figure 1** – SF-36 quality-of-life questionnaire scoring in 34 pulmonary arterial hypertensive patients under treatment with specific targeted (oral) therapies. In the vertical axis, 100 and 0 correspond respectively to best and poorest health.

(as an alternative to the generic ones) may be looked on as an important headway for a better understanding of patient's perspective, none can be considered as sufficiently complete. Dimensions such as hope, self-image, role changes, sexuality, self-efficacy and spirituality are hardly ever explored. Thus, while analyzing HRQOL, one must consider that no single questionnaire or combination of questionnaires is capable of capturing all aspects of patient's perspective.

Having in mind these methodological difficulties and limitations<sup>28</sup>, HRQOL has been shown to be severely depressed in PAH<sup>13,15,29</sup>. The tendency that we observed of a more impressive depression in physical domains is in agreement with the literature<sup>29</sup>. In the graph shown in Figure 2, the intercept indicates that for any given score associated with physical health, the corresponding mental component score tends to be higher. However, it must be acknowledged that the questionnaires, in general are particularly limited in their ability to assess specific dimensions of mental health<sup>28</sup>.

On the other hand, our observation of most scores above 50 is in contrast with other studies<sup>13,15,29</sup>, and may be explained by differences between patient populations. Notoriously, PAH associated with congenital heart disease (the majority of patients in this study) is a more insidious disease, and patients tend to be more adapted to their illness. This is in contrast with the rapidly progressive course of PAH associated with systemic sclerosis or idiopathic PH (the majority of cases in the mentioned studies). An interesting observation of ours was the lack of correlation between oxygen saturation and the quality of life. Lowest levels of oxygen saturation were observed in patients with PAH associated with congenital heart disease. The fact that some hypoxemic patients with Eisenmenger syndrome are relatively well adapted to daily tasks and satisfied with their quality of life is really intriguing, but frequently observed in clinical practice.

There has been general agreement that HRQOL does not correlate with hemodynamic abnormalities in PAH<sup>13-15,29</sup>. Even

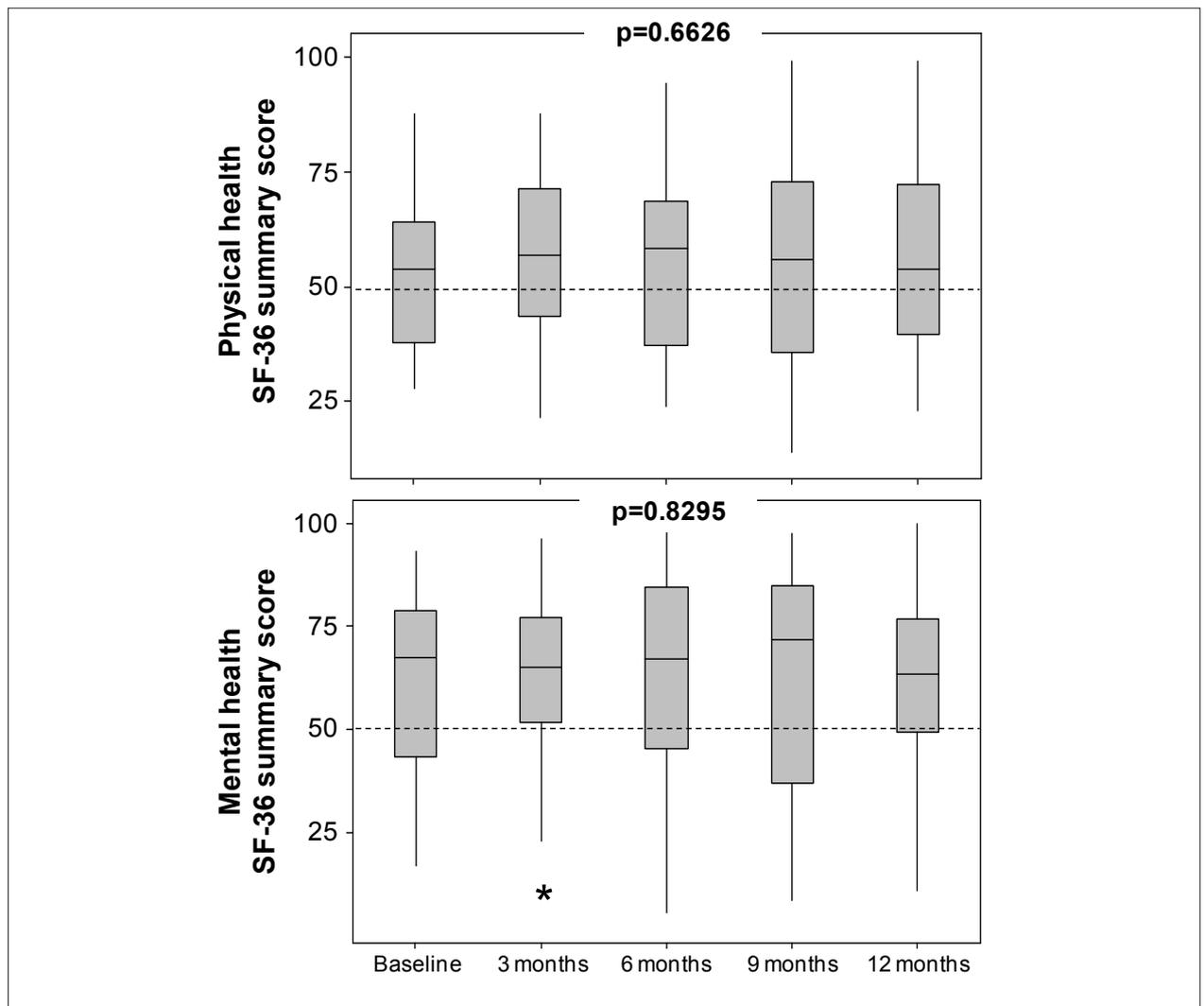


**Figure 2** – Association between the physical and mental components of health-related quality of life (SF-36 questionnaire) in 34 pulmonary hypertensive patients on specific targeted therapies. In both horizontal and vertical lines, 100 and 0 correspond respectively to best and poorest health.

**Table 2** – Functional data in 31 pulmonary arterial hypertensive patients followed for 12 months on specific therapies\*

	Baseline	3 months	6 months	9 months	12 months	p value
Functional class (N)						
II	23	22	20	17	17	
III	8	8	10	14	12	0.4663
IV	0	1	1	0	2	
Six-minute walk distance (meters)	420 (257-564)	387 (210-519)	411 (177-567)	407 (159-554)	432 (168-576)	0.2775
Peripheral oxygen saturation						
<i>Whole group</i>						
Resting	95 (63-98)	94 (72-98)	93 (69-98)	95 (61-98)	96 (64-97)	0.7346
6-min walk	86 (38-98)	84 (23-98)	84 (21-98)	87 (28-97)	85(26-97)	0.5471
<i>PAH-CHD (N=19)</i>						
Resting	89 (63-98)	90 (72-97)	91 (69-97)	89 (61-98)	89 (64-97)	0.9001
6-min walk	81 (38-97)	76 (23-96)	76 (21-96)	83 (28-96)	73 (26-96)	0.1124

\*Sildenafil (20 – 80 mg t.i.d.), bosentan (125 mg b.i.d.) or combination of both  
PAH-CHD: pulmonary arterial hypertension associated with congenital heart disease  
Results of numeric variables are presented as median value and range.



**Figure 3** – Physical and mental health (SF-36 questionnaire scoring) in 31 pulmonary arterial hypertensive patients who completed 12 months of follow-up. In the vertical axis, 100 and 0 correspond respectively to best and poorest health.

considering short-term studies aimed at testing the effects of specific PAH therapies, improvement of hemodynamic abnormalities is not always associated with improvement in HRQOL<sup>9</sup>. On the other hand, associations between HRQOL and measures of the functional status (namely, the functional class, the Six-minute walk distance and Borg dyspnea index) have been demonstrated more consistently, even though they are not so tight if one considers the coefficients of correlation<sup>13-15,29</sup>. Again, in PAH, it is the physical component of HRQOL that best correlates with measures such as the Six-minute walk distance<sup>13</sup>. Our study showed better physical health summary scores in patients in functional class II compared with those in class III, and a significant correlation between physical functioning and the Six-minute walk distance in three instances during the follow-up. An important observation however, was that significant associations of SF-36 scores with the Six-minute walk distance were present in only 30% of all possible ties. We moved forward to using logistic

regression as an attempt to identify a lower limit in terms of walked distance below which patients would have importantly depressed HRQOL. It became clear to us that although patients walking less than 235-280 meters during the test would very likely be markedly unsatisfied with their quality of life, significant dissatisfaction would be expressed even above this range, in view of the low sensitivity of prediction. The heterogeneity of the ROC curves shown in Figure 4 illustrates the difficulties in predicting aspects of the quality of life based on the exercise capacity.

Health-related quality of life has been explored as part of the overall treatment evaluation in PAH, although its understanding within the community remains underdeveloped. Improvement of HRQOL has been reported in patients on different modalities of treatment, including intravenous (epoprostenol), subcutaneous (treprostinil), inhaled (iloprost) and oral therapies (bosentan, sitaxsentan, ambrisentan and sildenafil)<sup>1-3,10-12,30</sup>. However, the effects of interventions do

**Table 3 – Associations between the Six-minute walk distance and the quality of life in 31 patients followed-up for one year\***

SF-36 categories	Baseline	3 months	6 months	9 months	12 months	
Physical component	Physical functioning	$r_s = 0.44$ $p = 0.01$	$r_s = 0.33$ $p = 0.06$	$r_s = 0.46$ $p = 0.009$	$r_s = 0.31$ $p = 0.08$	$r_s = 0.53$ $p = 0.001$
	Role physical	$r_s = -0.02$ $p = 0.90$	$r_s = 0.09$ $p = 0.62$	$r_s = 0.30$ $p = 0.09$	$r_s = 0.45$ $p = 0.01$	$r_s = 0.30$ $p = 0.09$
	Bodily pain	$r_s = -0.03$ $p = 0.87$	$r_s = 0.30$ $p = 0.09$	$r_s = 0.22$ $p = 0.22$	$r_s = 0.20$ $p = 0.27$	$r_s = 0.36$ $p = 0.04$
	General health	$r_s = 0.24$ $p = 0.19$	$r_s = 0.18$ $p = 0.31$	$r_s = 0.38$ $p = 0.03$	$r_s = 0.31$ $p = 0.08$	$r_s = 0.09$ $p = 0.62$
	Vitality	$r_s = 0.32$ $p = 0.07$	$r_s = 0.28$ $p = 0.12$	$r_s = 0.58$ $p = 0.0006$	$r_s = 0.30$ $p = 0.09$	$r_s = 0.50$ $p = 0.003$
Mental component	Social functioning	$r_s = 0.18$ $p = 0.32$	$r_s = 0.54$ $p = 0.001$	$r_s = 0.31$ $p = 0.08$	$r_s = 0.10$ $p = 0.58$	$r_s = 0.36$ $p = 0.04$
	Role emotional	$r_s = -0.01$ $p = 0.93$	$r_s = 0.05$ $p = 0.76$	$r_s = 0.41$ $p = 0.01$	$r_s = 0.27$ $p = 0.08$	$r_s = 0.38$ $p = 0.03$
	Mental health	$r_s = 0.19$ $p = 0.29$	$r_s = 0.23$ $p = 0.20$	$r_s = 0.31$ $p = 0.08$	$r_s = 0.21$ $p = 0.25$	$r_s = 0.26$ $p = 0.14$

\*Associations were tested by calculating the Spearman's  $r_s$  (Rho) coefficient

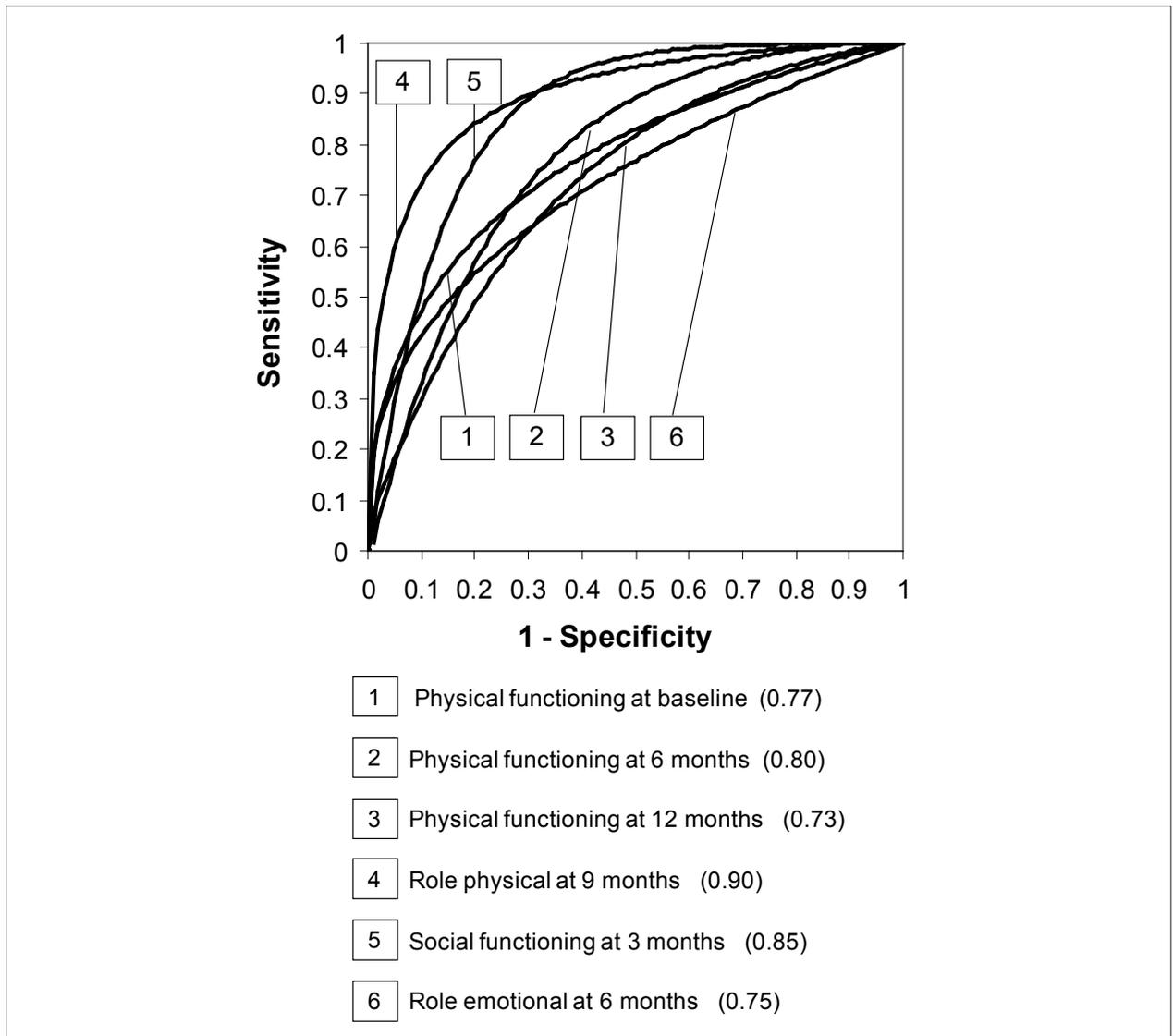
**Table 4 - Prediction of SF-36 scores  $\leq 25$  based on the Six-minute walk distance in pulmonary arterial hypertensive subjects**

SF-36 category	Six-min walked distance (meters)	P [score $\leq 25$ ]*	Sensitivity	Specificity	Odds ratio
Physical functioning at baseline	280	0.68	0.25	0.98	2.15
Physical functioning at 6 months	240	0.55	0.29	0.92	1.24
Physical functioning at 12 months	240	0.52	0.17	0.94	1.09
Role physical at 9 months	285	0.75	0.42	0.94	3.03
Social functioning at 3 months	236	0.50	0.13	0.96	1.01
Role emotional at 6 months	235	0.52	0.28	0.97	1.06

\*Probability of a score  $\leq 25$

not seem to be absolutely uniform, that is, they have not been reported in all studies<sup>9</sup>. Also, there have been differences in the same study when different questionnaires are used<sup>3</sup>. Furthermore, in some instances, changes have been reported for some, not for all domains of the same questionnaire<sup>10</sup>. Not infrequently, several modalities of treatment appear in the same HRQOL study<sup>13-15,29</sup>, but comparisons between treatments have only rarely been performed<sup>13</sup>. The way patients respond to treatments depends not only on the pharmacological effects of drugs, but also on factors such as the complexity of medication delivery (an infusion pump is needed for continuous intravenous epoprostenol administration), time of adaptation to therapy and the level of support from the

multiprofessional team<sup>28</sup>. Eventually, the type of medication may not be an important determinant of the quality of life<sup>13</sup>. In the present study, with two exceptions (fatal outcomes) patients on oral PAH therapies remained stable over one year of observation in terms of both exercise capacity and quality of life. The physical and mental component summary scores remained stable over the visits, with mental health a little better than physical health, the same way as observed at baseline. Again, the etiology of PAH (most patients with congenital heart disease and no patients with systemic sclerosis) may have played a role. On the other hand, it would not be ethical to analyze the specific role of chronic drug administration on patient's quality of life, for example by having a control group



**Figure 4** – Receiver operator characteristic (ROC) curves related to the prediction of the quality of life based on the exercise capacity (Six-minute walk distance, cut-off values shown in Table 4) in pulmonary arterial hypertensive patients on targeted therapies. For each of the SF-36 categories analyzed, the area under the curve is indicated.

of untreated patients with Eisenmenger syndrome (known to have a more insidious disease). In support to this view, a recent retrospective study involving a large cohort demonstrated the beneficial effects of advanced PAH therapies on the survival curves of patients with this syndrome<sup>31</sup>, thus emphasizing the need for specific medication.

Our study has two noticeable limitations. First, the patient population was relatively small. As a result, we were unable, for example to analyze HRQOL comparatively in PAH associated with congenital heart disease and idiopathic PAH. However, except for one patient who was lost to follow-up, all subjects were evaluated consistently and repeatedly over five visits to the hospital. This allowed us to comparatively analyze the exercise capacity and HRQOL all over the follow-up. On the other hand, because several etiologies of PAH were not included (connective tissue disease, chronic liver disease with portal hypertension,

anorectic agents use, human immunodeficiency virus infection, schistosomiasis and hemolytic anemia) we can assume that our patient population was not so heterogeneous. The second limitation was the use of a single HRQOL questionnaire, taking into consideration that two or three instruments have been used in other studies<sup>1-3,11,12</sup>. Unfortunately, in this way, we were limited by the number of instruments that are validated in the Portuguese language. Although the Minnesota Living With Heart Failure questionnaire, considered as a condition specific instrument<sup>32</sup> is validated, it cannot be looked on as PAH specific. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)<sup>33</sup> has been specifically designed for pulmonary hypertension, and can be considered as a valuable new instrument for assessing patient-reported outcome in routine practice. However, it is not validated for use in the Portuguese language yet.

Based on our observations, we would like to conclude that PAH patients initially in class II or III who remain functionally stable on specific oral therapies also do well in terms of their HRQOL. Domains related to physical health tend to be more impressively affected compared with mental health. Repeated measures over a period of 12 months showed that HRQOL was only partly related to the exercise capacity; significant associations were observed in only 30% of possible ties. Although patients walking less than 235-280 meters during the six-minute walk test generally have importantly depressed quality of life, significant dissatisfaction may be expressed above this range. Thus, HRQOL is not tightly associated with exercise capacity in PAH, particularly when it is evaluated over the medium term. Further studies are necessary for a better understanding of patient's perspective, possibly including instruments other than conventional questionnaires.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

### Study Association

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