

Six-minute walk test in pulmonary hypertension of any etiology

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The six-minute walk test is a sub-maximal exercise test that measures the exercise capacity in patients with pulmonary hypertension (PAH). It's easy, useful as a prognostic indicator and allows monitoring the effectiveness of specific treatments and monitor the natural course of the disease. Objective: To study the exercise capacity of all etiologies of PAH through the six-minute walk test and the changes and potential effects of drugs after 4 to 6 months. Measures: heart rate, O₂ saturation, blood pressure, end of the test and motive, specific treatments before and during the study, functional class New York Heart Association (NYHA) and mortality. Results: 58 participants, 6 (10.3%) died. 38 patients (65.5%) performed the first test, 34 (58.6%) the second test and 29 (50%) both, of them 14 (48.2%) improved in distance walked. The average distance traveled in the first test was 386.6 +128.1 meters (m) and the second 418.6 +103.1 m. This was higher in men in both tests ($p=0.049$, $p=0.006$). The number of patients in NYHA functional class III and IV was significantly lower in the second interview ($p=0.003$) and improvement in functional class NHA was associated with greater distances covered in the second test ($p=0.002$). Just the beginning of Sildenafil during the follow-up showed an improvement in the distance ($p=0.023$). The desaturations >10% in the first test were more frequent among patients who died ($p=0.032$). No etiology of PAH walked a significantly shorter distance.

The test of six minutes is the most common test for evaluating the capacity of exercise tolerance in patients with pulmonary hypertension (PAH). It has the advantage to be a simple exercise to perform, without the need for sophisticated equipment and the lack of invasiveness, and can be repeated to monitor the clinical evolution. It also allows an assessment of the response to the different treatments.

Serves as predictive for the survival of these patients. Existing direct correlation with the cardiovascular functional status and inverse correlation with the pulmonary resistance, but not with mean pulmonary arterial pressure. Also correlates positively with the peak of maximum O₂ consumption (VO₂ max) during exercise (1). Also, the decrease in arterial O₂ saturation of more than 10% during the six minutes of the test involves an increased risk of mortality of 2.9 (2-4). It has been shown that distances of less than 325 meters (m) (5), TA systolic <120mmHg during the test (6), VO₂ <10.4 ml / kg / min or NYHA functional class III and IV in the initial assessment of the PHA, imply data of bad prognosis (2), although most of these studies are performed in patients with PAH of idiopathic etiology, familiar or associated with connective tissue diseases.

Therefore, we propose to undertake a study to assess the functional status of patients with PAH from any source, using the six-minute walk test, as well as the variation of the same and the influence of possible treatments after a period of 4-6 months.

Material and methods

This is a prospective longitudinal descriptive study. The start of the follow-up period begins from June 1, 2006, when it began to conduct clinical surveys for patients who accepted telephonically the inclusion in the study. Previously these patients were diagnosed of severe PHA according to the existing guidelines nowadays (2,7,8).

In these interviews, up to date clinical data was collected from the patient, the current treatment and a six-minute walk test was performed for an initial functional assessment.

After a period of not less than 4 months (except death or abandonment of the study), there was a new interview, in which it was re-assess the same parameters, new test of 6 minutes was performed, and it was accounted incomes and changes of treatment if there had been.

1. Pulmonary arterial hipertensión (PAH).	
1.1. Idiopathic.....	7(12,1%)
1.2. Familiar.....	1 (1,7%)
1.3. Associated with PAH:	
- Collagen vascular disease.....	2(3,4%)
- Congenital systemic to pulmonary shunts.....	1(1,7%)
- Portal hipertensión.....	2(3,4%)
- HIV infección.....	1(1,7%)
- Drugs and toxins.	
- Other (thyroid disease, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobincopathies, myeloproliferative disorders, splenectomy.....	1(1,7%)
1.4. Associated with significant venous or capillary involvement	
- Pulmonary veno-occlusive disease (PVOD).	
- Pulmonary capillary Hemangiomas (PCH).	
1.5. Persistent PH of the newborn (PPHN).	
2. Pulmonary venous hipertensión.	
2.1. Left-sided atrial or ventricular heart disease.....	3(5,2%)
2.2. Left-sided valvular heart disease.....	29(50%)
3. Pulmonary hipertensión associated with intrinsic lung disease or hypoxemia	
Chronic obstructive pulmonary disease (COPD).	
3.1. Chronic obstructive pulmonary disease.....	1(1,7%)
3.2. Interstitial lung disease.....	3(5,2%)
3.3. Sleep-disordered breathig.	
3.4. Alveolar hypoventilation disorders.....	1(1,7%)
3.5. Chronic exposure to high altitude.	
4. Pulmonary hipertensión caused by chronic or embolia disease.	
4.1. Thromboembolic obstrucción of proximal pulmonary arteries.....	2(3,4%)
4.2. Thromboembolic obstrucción of distal pulmonary arteries.	
4.3. Pulmonary embolism (tumor, parasites, foreign material).	
5. Miscellaneous. Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)-	
	(1,7%)
6. Without final diagnosis.....	3(5,2%)

The follow-up ended when the patient completed the study, died, or when he refused to continue either by telephone or because of absence.

The walking test was made in a corridor of 76 m in length with subdivisions every 6 m, and all of them made by the same investigator.

For its implementation ATS recommendations were followed (9). Prior to the start of the test there were 10 minutes of rest, in which the heart rate (HR), blood pressure (BP) and arterial oxygen saturation were measured. Later, they started walking up to the maximum of possibilities for 6 minutes monitoring heart rate and oxygen saturation and at the end of the test, after one minute of recovery, the same data were measured. In addition to that, it was picked up if the patient finished or not the test and the reason, and it was calculated the maximum O₂ consumption (VO₂ max):

$$0.1 \text{ ml / kg / min} \times \text{distance (m)} / +3.5 \text{ ml / kg / min Time (min)}.$$

The data were analyzed using the statistical program SPSS 11.5. Initially it was performed a descriptive statistics of the data, obtaining the following parameters for each variable: measures of central tendency (arithmetic mean), measures of dispersion (standard deviation, range and variance), minimum and maximum values.

All values of p are bilateral, and the statistical significance used was p < 0.05.

Categorical data was analyzed using the chi-square test or Fisher's exact test, as it was more appropriate.

If the variables satisfy the conditions of normality (Kolmogorov-Smirnov test and Shapiro-Wilks test) and homocedasticity (equal variances using Levene test), it was used the t-student test for the comparison of means, and if this was not the case, the Mann-Whitney U was used.

In the case of determinations of the same quantitative variables at two different times, it was used the Wilcoxon test for related data, or t-student for paired data, according to whether they meet or not conditions of normality and homocedasticity.

Among the quantitative variables it was used the Pearson correlation analysis when the data followed a normal distribution and Spearman when they were not.

Results

Data were collected from 58 patients, 32 females and 26 males, mean age 63.88 + 11.88 years. Of them, 75.9% of patients had more than 60 years. The etiology of PAH is shown in Table 1.

The average time elapsed between the first and second visit was 5.1 + 4.4 months (range from 1 month to 21 months). The end of follow-up occurred in 71.4% (n = 40) for completion of the study with the second interview, 19.6% (n = 11) because of patient refusal to continue and 10.3% (n = 6) because of death. Of these, 50% (n = 3) died of respiratory failure, 16.6% (n = 1) for heart failure and 33.3% (n = 2) for other reasons: massive bleeding and liver failure.

Functional class for dyspnea in both interviews, expressed according to the New York Heart Association (NYHA) is shown in Figure 1. On the second visit, in case of death of the patient, was taken as the functional class the one they had in the days before it. Also in cases of abandonment of the study by the patient, it was taken that functional class present at the time.

The 24.1% of patients (n = 14) improved the functional class from the first to the second visit, being lower the number of patients in NYHA functional class III or IV at the second visit (p=0.003). The presence of functional class III or IV was not significantly associated with a higher frequency of death in the first or second visit (p=0.087 and p=0.072 respectively).

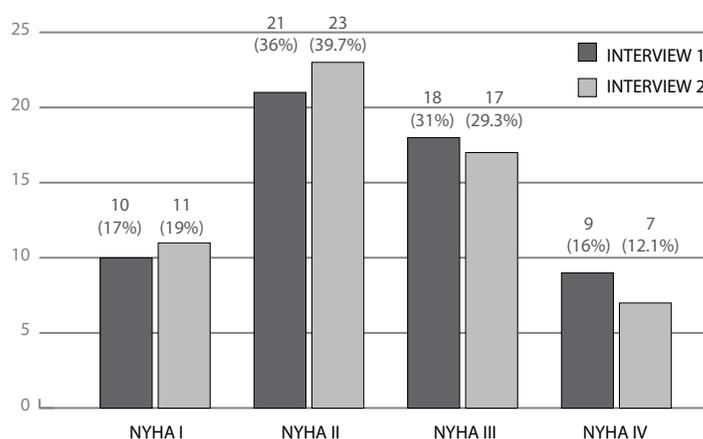


Figure 1: NYHA functional class in 1st and 2nd visit.

Most patients in our series had a prior entry related to pulmonary hypertension (dyspnea, chest pain of no coronary characteristics ...) with a median of 3.3 + 3.9 entries per patient. Also during the relatively short follow-up between the first visit and the end of the study, 45 entries in 58 patients occurred (0.7 + 0.8 revenue per patient).

Only 12.06% (n = 7 patients) of the study population had one of the specific treatment of PAH in the first visit. Of which, antagonists of endothelin receptors 6.9% (4), were the most frequent, followed by sildenafil 3.4%(2) and prostacyclins 1.7% (1). Only 1 patient carried a combination of treatments (1.7%) with sildenafil and prostacyclins. During the study, 8 specific PAH treatments were added (5 sildenafil, 2 antagonists of receptors of endothelin and 1 prostacyclin).

At the end of the study at the second visit, 13.8% (n = 8 patients) had a specific treatment of PAH. Of these 7 patients (12.1%) with sildenafil, 3 patients (5.2%) with antagonists of receptors of endothelin (in 3 other occasions this treatment was removed, on two occasions they had it in the first visit and it is modified and on another occasion was removed because of intolerance by the patient) and 2 patients with prostacyclins (3.4%). 4 patients took combined treatment (6.9%), 2 took sildenafil and antagonist of the receptors of endothelin, and 2 prostacyclin and sildenafil) Figure 2.

Regarding the need for oxygen treatment, 24.1% (14) had taken it in some occasion, 10.3% (6) had it in the first interview and in 3 cases (5.2%) the treatment was added during the study. The 6 minutes tests were carried out without this contribution.

The first walking test could be made in 65.5% of patients (n = 38), whereas it was not possible in 34.5% (n = 20), because of poor NYHA functional class in 55% (11) and because of denying access to its implementation in 45% (9).

The second test was carried out on 58.6% of patients (n = 34), and it was not possible in 41.4% (n = 24), because of poor NYHA functional class in 33.3% (8), because of denying access to its implementation in 45.83% (11) and because of death in 20.8% (5). The results obtained in both tests are shown in Table 2.

Both six-minute walk test were done by a total of 29 patients (50%) of which 14 patients increased the meters walked from the first to the second (48.2%) 2 did the same meters (3.4%) and 13 decreased the distance (22.4%).

There were 8 patients (13.8%) who did the first test and not the second (4 for poor functional class, and 2 because they refused to do so, the 2 remaining died).

Parameters	First six-minute walk test	Second six-minute walk test
Finished test	YES 34 (89,5%) NO 4 (10,5%)	YES 33 (97,1%) NO 1 (2,9%)
Reason of unfinished test	- Dyspnea 3(75%) -Bradycardia 1(25%) - Chest pain, Tachycardia ó Near syncope 0 (0%)	- Dyspnea 1(100%)
Heart rate at rest freq.	Min 55 Max 120 Mean 79,4+16,5	Min 54 Max 118 Mean 78,7+14,9
Oxygen saturación at rest (%)	Min 89 Max 99 Mean 95+2,8	Min 90 Max 98 Mean 96+2,1
Distance (meters)	Min 120 Max 610 Mean 386,6+128,1	Min 232 Max 610 Mean 418,6+103,1
Minimal oxygen saturación (%)	Min 65 Max 98 Mean 89,1+7,9	Min 80 Max 98 Mean 92,3+4,5
Maximum systolic blood pressure (mmhg)	Min 110 Max 190 Mean 142,4+19,6	Min 110 Max 180 Mean 143,8+21,1
Maximum heart rate. (lpm)	Min 77 Max 195 Mean 120,2+27	Min 63 Max 180 Mean 119,7+27,1
Maximum oxygen consumption (vo2 max) (ml/kg/min)	Min 6,5 Max 25,1 Mean 13.4+3,1	Min 9,3 Max 25,3 Mean 14+2,6

Table 2: Six-minute walk test results.

In 3 cases (5.2%), the second test was performed without being able to do the first, being the three times for poor functional class that improved from the first to second visit.

The distance walked was greater in men in both the first and the second test (p=0.049 and p=0.006).

It was observed statistically significant correlation between the meters walked and the height 0.351 (p=0.031) but not with age or body mass index.

No etiology was found that walked less than 325 meters with more frequency than the rest.

We compared the measurements of the parameters in the first and second test finding that the minimal saturation O₂ was higher in the second test of 6 minutes in a meaningful way with respect to the first (p=0.021).

Taking into account the parameters of the six-minute walk test, as is described in the literature, are associated with poor prognosis (decrease of O₂ saturation in more than 10% during the test; distance walked less than 325 m; Consumption O₂ <10.4 ml / kg / min and TA systolic <120 mmHg during the test) we analyzed by Chi-square test or Fisher's exact test depending on the data. Among the deceased patients it was observed a higher frequency of desaturations > 10% in the first test of 6 minutes (p=0.032) but not in the second walking test (p=1).

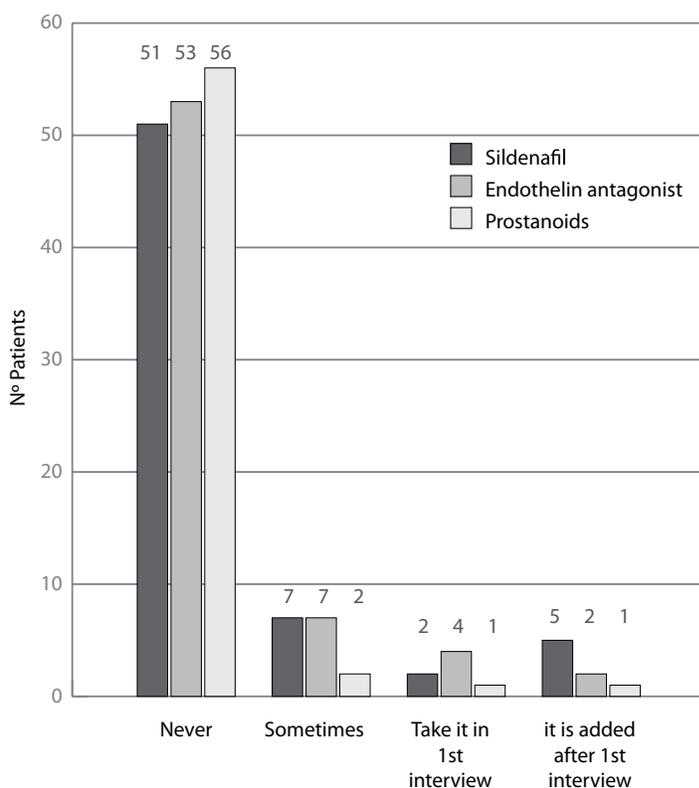


Figure 2: Specific Drugs of pulmonary hypertension in our series

Regarding the relationship of the NYHA functional class with the parameters measured in the walking test, we find that the improvement of functional class from first to second visit was significantly associated with a greater distance walked in the second test ($p=0.002$). Also, patients in advanced functional class (III or IV) walked a distance significantly smaller in both the first and the second walking test ($p=0.006$ and $p=0.028$). The saturation of the minimum O₂ was significantly lower in patients with NYHA III or IV in the first test ($p=0.001$).

With regard to treatments in relation to the distance walked in the six-minute walk test, we observed that patients treated with O₂ at home in some occasion, walk more often distances of less than 325m in the first test ($p=0.014$). This data was not significant in the second test because of the 5 patients who walked <325 m in 2nd walking test had only taken O₂ some time ($p=0.228$).

Also in patients who were treated with sildenafil after the first visit it was observed an improvement in meters walked from the first to the second walking test ($p=0.023$). Was not significant the start of other treatments.

Correlation study was performed between the systolic pressure of pulmonary artery (PASP) measured by echocardiogram and hemodynamic study (Table 3) and data obtained in tests of 6 minutes (Total meters traveled, maximum heart rate, minimal saturation O₂ and maximum O₂ consumption). There was a negative correlation between the systolic pressure of pulmonary artery (PASP) measured by echocardiogram and minimal saturation O₂ during the first test of 6 minutes (-0.368 ($p=0.029$)) (Figure 3).

It was also found a positive correlation between total meters walked in the first test of 6 minutes and minimal saturation O₂ obtained during this test: 0.439 ($p=0.006$) (Figure 4).

Discussion

A review of the literature shows that the normal walking speed is 83 m / min (10). It has also been proposed regression equations to predict the six meters walked in healthy adults (11).

According to this study in 173 healthy men and 117 women between 40 and 80 years of age, the average distance traveled was 576m for men and 494m for women, with a variance of 42% and 38% in the 6 minutes test respectively.

It should be considered factors that generate variability of the test: 1) reduce the distance traveled: Old age, female sex, obesity, low height, lung disease, cardiovascular and musculoskeletal, cognitive impairment, short hallway. 2) Increase the distance traveled: being tall, male sex, high motivation, prior experience in the test, long corridor and supplementation of oxygen in patients with exercise-induced hypoxemia (11).

In our study, the average distance walked was 386.6 ± 128.1 in the first test and 418.6 ± 103.1 in the second test of walking. Both values below those considered normal, but higher than that expressed in other studies (12-14) Table 3. This may be due to the higher percentage of patients in advanced functional class (III and IV) within those studies,

as these classes demonstrate a significantly lower number of meters traveled than with functional classes I and II in our study as in others as the French registry (12).

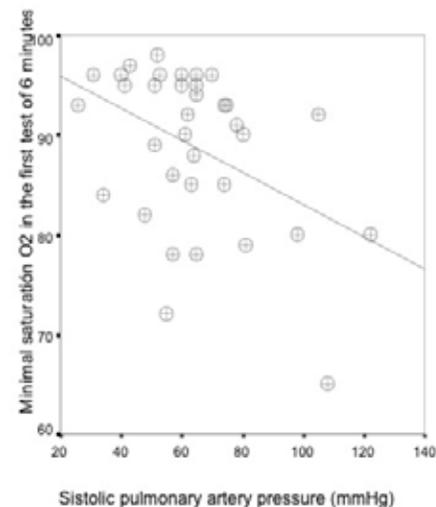


Figure 3: Graph of clouds of points showing the inverse correlation between the sPAP by echocardiogram and the minimal saturation O₂ in the first test of 6 minutes.

Although two large prospective series have confirmed the importance of the NYHA functional class as a prognostic variable (15,16), most of the published studies refer to it at the time of diagnosis of PAH, being often patients with idiopathic etiology or familiar and less frequent in other causes. The percentages of advanced functional class are high in those patients who have not yet begun treatment (12,13) (75% in class III or IV at diagnosis in the French Registry or 72.4% in an American series).

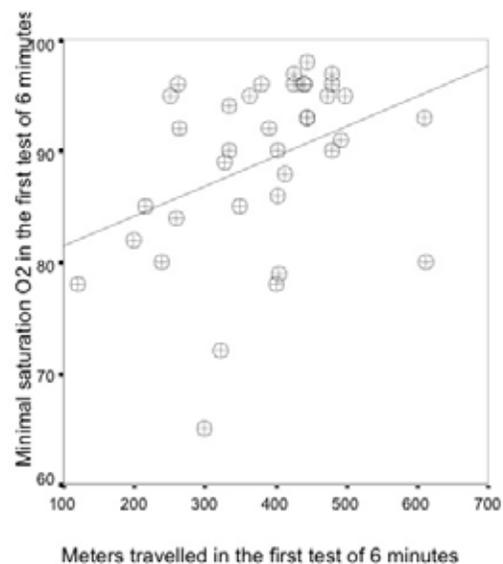


Fig 4: Graph of clouds of points showing the direct correlation between the traveled meters and the minimal saturation O₂ in the first test.

In our series all etiologies of PAH are collected and in some cases patients had already been treated for his illness, which modifies the average age and functional class.

Even so, the percentage of patients in advanced functional class III or IV on the first visit is high (47%). This may be related in part to the high number of patients with advanced valvular heart diseases joined to patients newly diagnosed untreated. Besides the high percentage, some patients had been admitted to periods close to the first visit and it is a voluntary testing which could explain in a way that 34.5% of patients did not conduct the first six-minute walk test.

The fact that a 24.1% improved in functional class from first to second visit may be due to initiation of specific treatments for PAH in some patients, or the solution or improvement of the cause of PAH, such as the valve replacement, which was performed 5 times during our follow-up or treatment of hyperthyroidism.

A study that describes that oxygen supplementation during exercise in patients with COPD or interstitial disease, increase a mean of 83 m (36%) on the distance walked in the 6 minutes test (17). Also other international study conducted in COPD patients, says that taking the inhaler with corticoids prior to the walking test increases a mean of 33m (8%) that distance (18).

Our patients did the test without the addition of O₂, or immediately after taking the inhaler, so we do not know if it had been able to influence the distance traveled. There was a statistically significant direct correlation between distance walked and the minimum oxygen saturation obtained during the test 0.439 ($p=0.006$), what confirms that with better oxygenation a longer distance is walked (Figure 4).

Several authors have demonstrated the high prognostic value of test of 6 minutes in the PAH, although different distances are proposed as a marker of poor prognosis. In one of the first controlled studies of PAH a distance <150 m was associated with very poor prognosis (19). Miyamoto et al showed that patients who walked <332 m had a lower survival rate than those who walked greater distances (20). Another study found a 18% reduction in risk of death for each 50 m walked in patients with idiopathic PAH (4) and Sitbon et al reported that patients in functional class III or IV NYHA walking <250 m before the start of treatment with epoprostenol or <380 m after 3 months treatment with epoprostenol have a worse prognosis than those who walk greater distances (21). The fact of choosing 325 m as cutoff point for our study may be equally valid, as it is presented in the recent literature on patterns of activity in this disease (5) we decided to use it in our series.

Although some series show different distances according to the etiology of PAH (12,13), we do not have a large number of cases so as to assess this, and we did not find any etiology that was significantly associated with a traveled distance less than 325 m.

The studies that have evaluated the usefulness of the test of 6 minutes have shown varying results (22-26). Although this test is easy to implement, most patients apparently do work less (sub-maximal effort) compared to cycle-ergometer.

In patients with COPD, some studies have found no significant differences in maximum minute ventilation and VO₂ between effort tests

in cycle-ergometer and walking 12 min (23). Similar findings have also been described in patients with severe heart failure (24-26). Based on these results some authors suggest that at least in patients with advanced cardiopulmonary, distance traveled during the walking test (usually seen as a capacity index of sub-maximal effort), probably reflects the capacity of maximum effort.

Regarding other parameters of poor prognosis, although there were no significant findings with respect to O₂ consumption and blood pressure among the deceased patients in the study, it was observed a higher frequency of desaturations > 10% in the first 6 minutes test ($p=0.032$). Not the same thing happened in the second walking test ($p=1$) (probably because only 1 of the patients who died during the study did the second test).

In our series, higher levels of sPAP measured by echocardiogram correlates with lower results of minimal saturation O₂. This is logical since the exchange of O₂ is worse with higher PAP, from there the predictive value of the 6 minutes test. The failure to not find statistical significance with the sPAP measured by hemodynamic study may be due to fewer measurements made by this method.

Although in our study it was done 2 times the test of 6 minutes, this did not help at times to assess the response to specific treatments for PAH, because there was not a prior test to initiation of the treatment and patients already were taking medication in our first visit. Hence we could only assess the cases in which treatment was initiated after the first visit or when a 6 minutes test was done before the start of the new treatment.

Thus, it has been objectified in our sample that patients who began treatment with sildenafil improved the distance traveled after the first visit from the first to the second test of 6 minutes ($p=0.023$). Of the 5 treatments started 4 of them increased the number of meters traveled in an average of 131 m (minimum 35 m, maximum 280 m) and remaining patient died before being able to conduct the second test. This is consistent with studies supporting the use of sildenafil (27,28). Distances described in these studies vary from 47 m to 154 m according to different etiologies, ages and doses employed. This is why the comparison is difficult, since in our case the etiology of our patients were varied (two idiopathic, one familiar, one associated with pulmonary fibrosis, and other associated to collagen diseases).

Different studies have shown improvement in the functional class after initiation of treatment (27-30). We have not found that the initiation of any specific treatment of PAH was significantly associated with improvement of functional class. However there is a trend to improvement in the initiation of treatment with sildenafil ($p=0.085$). Perhaps these data are influenced by the low number of registered specific treatments, and studies and monitoring are necessary to show that broader trend.

TABLE 3. CLINICAL AND HEMODYNAMIC DATA AT CLINICAL TRIALS OF PULMONARY HIPERTENSIÓN.

	HCU Lozano Blesa (Ridruejo)	NIH REGISTER (Rich et al)	FRENCH REGISTER (Humbert et al)	CHILE REGISTER (Zagolin et al)	PHC REGISTER (Thenappan et al)
NUMBER OF CASES	58	187	674	29	578
MULTICÉNTER	NO	YES	YES (17 hosp)	NO	YES
PERIOD	JUN 06- JAN 08	1 JUL 1981 -30 SEPT 1985	OCT 02 –OCT 03	JUN 03 –MAR 05	2004-2006 (1982-2006)
SPECIFIC TREATMENTS	YES,	NO	NO	NO	YES
MEAN AGE	63,88 + 11,8	36,4 + 15	50 + 15	40,5 + 14	48 + 14
% WOMEN	55,2%	63,1%	65,3 %	86,2 %	77 %
NYHA III-IV	47 %	71 %	75 %	72,4 %	80 %
SIX-MINUTE WALK TEST DISTANCE (m)	386,6 + 128	—	329 + 109	377,88 + 113	289 + 186
HEMODYNAMIC DATA:					
-RAP (mmHg)	9,4 + 5,94	9,7 + 6	8 + 5	8,07 + 6,5	11 + 7
-sPAP (mmHg)	66,5 + 22,5				
-mPAP (mmHg)	42,1 + 12,81	60 + 18	55 + 15	59,4 + 12	52 + 14
-cPAP (mmHg)	23,3 + 9,47		8 + 3		
-CI (L/min/m ²)	2,4 + 0,86	2,3 + 0,9	2,5 + 0,8	2,57 + 0,88	2,3 + 0,9
-RVPI (U W)	11,27 + 5,86	26 + 14	20,5 + 10,2	22,48 + 10,69	
INCLUSIÓN CRITERIA	sPAP >60 mmHg (echocardiogram)	mPAP> 25mnHg or> 30 mnHg at rest in cardiac catheterization. Idiopathic and familial HTP were included by them. It excludes the rest.	mPAP>25 mnHg at rest and cPAP< 15mmHg in cardiac catheterization . They are excluded patients by pulmonary severe pathology (FEV1<60%; CVF<60%) and cardiac not congenital disease	mPAP> 25mnHg at rest, or > 30 mmHg in exercise in cardiac catheterization, in absence of paremchyma pulmonary or cardiac left disease.	mPAP> 25mnHg at rest, or > 30 mmHg in exercise in cardiac catheterization, in patients of the group I of HTP. Patients are excluded by nailed cPAP> 15 mmHg, Pulmonary disease (FEV1/CVF <70 %), interstitial disease and TEP.

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