Validation of a treadmill six-minute walk test protocol for the evaluation of patients with pulmonary arterial hypertension*

Validação de um protocolo para o teste de caminhada de seis minutos em esteira para avaliação de pacientes com hipertensão arterial pulmonar

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Abstract

Objective: To develop and validate a protocol for the treadmill six-minute walk test (tread6MWT) to evaluate patients with pulmonary arterial hypertension (PAH). **Methods:** The study population comprised 73 patients with PAH, diagnosed by means of right heart catheterization, with or without NO inhalation. All patients performed a hallway 6MWT and three tread6MWTs based on a pre-determined incremental speed protocol and interposed by a rest period. The patients who had been submitted to hemodynamic testing using NO performed the third tread6MWT while inhaling the same dose of NO that had been used during the catheterization. **Results:** We found that the treadmill six-minute walk distance (tread6MWD) correlated with hemodynamic data, functional class and the hallway six-minute walk distance (6MWD). In addition, the tread6MWD correlated significantly with survival, thereby confirming the correlation with disease severity. Inhalation of NO during the tread6MWT led to variations that were consistent with the hemodynamic changes induced by the same dose of inhaled NO, suggesting that the protocol developed can reflect the effect of therapeutic interventions. **Conclusions:** We conclude that the tread6MWD is a useful prognostic and functional marker for the routine evaluation of PAH patients.

Keywords: Hypertension, pulmonary; Exercise test; Hemodynamics.

Resumo

Objetivo: Elaborar e validar um protocolo para teste de caminhada de seis minutos em esteira (TC6est) para a avaliação de pacientes com hipertensão arterial pulmonar (HAP). **Métodos:** A população do estudo foi composta por 73 pacientes com HAP diagnosticados através de cateterismo cardíaco direito, com ou sem inalação de NO. Todos os pacientes realizaram um TC6 em solo e três TC6est baseados em um protocolo de incremento de velocidade pré-determinado e intercalados por um período de repouso. Os pacientes que haviam realizado o teste hemodinâmico com inalação de NO realizaram o terceiro TC6est com a inalação da mesma dose de NO utilizada durante o cateterismo. **Resultados:** Os resultados mostraram uma correlação da distância caminhada no TC6est com os dados hemodinâmicos, assim como com a classe funcional e com a distância caminhada no solo. Além disso, a distância percorrida no TC6est apresentou uma correlação significativa com a sobrevida, confirmando, portanto, sua correlação com a gravidade da doença. A inalação de NO durante o TC6est levou a variações compatíveis com as variações hemodinâmicas frente à mesma dose de NO, sugerindo que o protocolo em questão pode refletir o efeito de intervenções terapêuticas. **Conclusões:** Concluímos que a distância percorrida no TC6est é um marcador funcional e prognóstico na avaliação de rotina de pacientes com HAP.

Descritores: Hipertensão pulmonar; Teste de esforço; Hemodinâmica.

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Introduction

In recent years, there have been increasing advances toward a deeper understanding of the pathophysiology of pulmonary arterial hypertension (PAH).[1] The therapeutic advances in PAH resulting from this better understanding call for objective measures to evaluate the efficacy of the different classes of medication that are currently available or being developed.[2]

In clinical trials, the six-minute walk test (6MWT) is the most widely used functional marker, because it is a simple test that correlates with the hemodynamic variables and with the results of cardiopulmonary exercise testing, as well as having a prognostic value for the evaluation of PAH patients.[3,4] The 6MWT should be performed in a hallway of approximately 30 m in length, flat and free of traffic, which limits its routine use in various facilities. The use of shorter distances decreases the reproducibility of the test, which is due, among other reasons, to the number of turns the patient must make.[5]

The treadmill six-minute walk test (tread6MWT) is a variation of the 6MWT that allows physical examination to remain simple, i.e., based on the act of walking, without any of the limitations imposed by the need for a long, free hallway. The tread6MWT can also be used when there is a need for acute intervention or for closer monitoring of physiological variables. The comparison between the original (hallway) 6MWT and the tread6MWT in COPD patients has demonstrated that, although the tread6MWT is not comparable to the 6MWT in terms of the distance covered, it is a satisfactory alternative for the functional evaluation of COPD patients.[6] However, various factors should be considered before conducting the tread6MWT, e.g., whether or not to develop an incremental speed and inclination protocol and whether the speed should be controlled by the patient or the technician responsible for the examination.

To date, there have been no reports regarding the development of protocols for the tread6MWT to evaluate PAH patients. The objective of this study was to develop and validate a protocol for the tread6MWT to evaluate PAH patients.

Methods

Seventy-three PAH patients not having previously used any specific medication, monitored at the Pulmonary Circulation Outpatient Clinic of the *Instituto do Coração* (InCor, Heart Institute) of the University of São Paulo School of Medicine *Hospital das Clínicas*, between April of 2003 and January of 2007, were included in the present study. The diagnostic investigation was conducted according to the Brazilian guidelines for the management of PAH,[7] and the diagnosis of PAH was invasively confirmed by right heart catheterization.

The study protocol was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas*.

The protocol was performed in two phases:

- Preliminary phase (pilot study), including 14 patients, in which the learning curve for the tread6MWT protocol was determined.
- Study phase, in which patients were divided into two groups according to whether or not they had performed the acute test with NO inhalation during right heart catheterization in the preliminary phase. Fifty-nine patients were included in this phase. Of those, 39 were included in a subgroup of patients that performed the acute test with NO inhalation (the NO group), and 20 were included in a subgroup of patients who did not perform the acute test (the non-NO group).

For the overall analysis of the study, the patients who participated in the preliminary phase were included in the non-NO group. Therefore, the sample comprised 73 patients, 39 in the NO group and 34 in the non-NO group, as shown in the algorithm (Figure 1).

All patients were submitted to hemodynamic testing by inhaling oxygen at a concentration of 24% via a Venturi mask (Hudson, Durham, NC, USA), in the supine position. Each patient was catheterized using a 7F pulmonary artery cath-

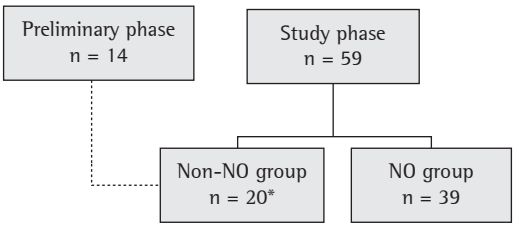

Figure 1 - Study design. *The patients who participated in the pilot study were included in this group, resulting in a total of 34 patients.

eter (Baxter Health Corporation, Irvine, CA, USA). Cardiac output was measured using the thermodilution technique. The minimum criterion for the diagnosis of PAH was a mean pulmonary artery pressure greater than 25 mmHg and pulmonary wedge pressure lower than 15 mmHg, which are characteristic of precapillary PAH.[8]

The acute test using a vasodilator was performed in the subpopulation of patients with idiopathic PAH who had never performed such a test, as well as in the subgroup of patients with schistosomiasis, through the inhalation of NO at a concentration of 40 ppm, added to the oxygen delivered by the Venturi mask for a period of 10 min; after stabilization, new hemodynamic measurements were taken in order to evaluate patient response.[9,10] We chose to use the Venturi mask to deliver NO because it was necessary to ensure a less variable fraction of inspired gases, even when an increased minute volume was expected, e.g., during the exercise test with NO inhalation.

Responders were defined as the patients who presented a reduction in mean pulmonary artery pressure of at least 10 mmHg, reaching levels lower than 40 mmHg and maintaining or increasing cardiac output.[9,10]

Functional capacity was evaluated based on the 6MWT results, the functional class and the tread6MWT results.

The 6MWT was performed according to the recommendations of the American Thoracic Society,[5] and the six-minute walk distance (6MWD) was recorded regardless of pauses during the test.

The functional capacity of the patients was determined according to the New York Heart Association classification,[7,8] adapted for PAH.

In order to perform the tread6MWT, patients were required to walk on a treadmill (Medtrack ST; Quinton, Seattle, WA, USA), set at the normal inclination.

Patients began at a speed of 2 km/h and were asked, every 30 s, whether the speed should be increased, maintained or decreased. With the permission of the patient, the speed was increased by 1 km/h, the maximum speed not exceeding 8 km/h; after the maximum speed had been reached, the speed was either maintained or decreased by 0.5 km/h, according to the wishes of the patient.

Respiratory rate (RR), SpO_2, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before and after the test. Throughout the test, HR and SpO_2 were monitored. After the test, the treadmill 6MWD (tread6MWD) was recorded.

Throughout the entire test, patients were maintained on the Venturi mask to ensure a FiO_2 of 24%. After a 15-min rest break, which allowed the physiological parameters (HR, RR, SBP, DBP and SpO_2) to return to baseline levels, patients were submitted to a second test under the same conditions. During the rest break, patients were maintained on the Venturi mask.

During the preliminary phase of the protocol, after a second 15-min rest break, patients were submitted to a third tread6MWT, beginning at the same baseline levels. This third test was performed in order to determine the learning curve.

Table 1 - Clinical, functional and hemodynamic data from the sample as a whole (n = 73).

Variables	Results
Age, years	40 ± 11
Gender (Female:Male)	2.6:1.0
Functional class (I-II:III-IV)	1.0:1.2
Systemic arterial pressure	
Systolic, mmHg	114 ± 12
Diastolic, mmHg	81 ± 11
Respiratory rate, breaths/min	19 ± 6
Heart rate, bpm	88 ± 14
SpO_2, %	95 ± 4
Six-minute walk distance	
Hallway, m	436 ± 127
Treadmill, m	372 ± 121
Invasive hemodynamic testing data	
Right atrium pressure, mmHg	10 ± 7
Pulmonary wedge pressure, mmHg	11 ± 4
Mean pulmonary artery pressure, mmHg	60 ± 20
Cardiac output, L/min	4.42 ± 1.64
Pulmonary vascular resistance, Woods units	13 ± 10
Diagnosis	
Idiopathic pulmonary artery hypertension, n (%)	39 (54)
Schistosomiasis, n (%)	20 (28)
Connective tissue diseases, n (%)	8 (11)
Congenital cardiopathies, n (%)	6 (7)

Mean ± SD, except where noted.

After having performed two tread 6MWTs with oxygen only, the patients who had been submitted to NO inhalation during invasive hemodynamic testing (the NO group) performed the third tread6MWT, with the addition of inhaled NO, also at 40 ppm, to the Venturi mask, as during the invasive hemodynamic testing.

After the second tread6MWT, there was a second 15-min rest break, during which patients were maintained at an oxygen concentration of 24%, with the addition of NO at a concentration of 40 ppm, via the Venturi mask. After the rest break, the tread6MWT was performed again with inhaled NO at the same concentration, delivered by the Venturi mask.

Continuous data are presented as means and standard deviations, whereas categorical data are presented as percentages. For the analysis of correlation between the variables obtained during the tread6MWT and the remaining variables, the Pearson method was used. To compare the three tests performed, we used ANOVA for repeated measures. The Bonferroni test was used for post hoc analysis. Survival in function of time was described by Kaplan-Meier curves. After having determined the survival in function of the median of the tread6MWD, the curves were compared using the log-rank test. Values of $p < 0.05$ were considered statistically significant.

Results

The clinical characteristics of the 73 patients included in the present study are shown in Table 1. The mean age, the predominance of the female gender and the degree of hemodynamic impairment were in accordance with previously published data on PAH patients.[11-13]

In order to analyze the learning curve related to the protocol for the tread6MWT, three measurements were taken, under identical conditions, in the preliminary phase. The comparison between the distances covered on each of the three tread6MWTs, in which patients inhaled only oxygen at a concentration of 24%, is shown in Figure 2a.

There was a significant difference between the first and second tread6MWTs in terms of the tread6MWD, although there was no such difference between the second and third tread6-MWTs. In view of these results, two tests with oxygen inhalation were then performed in order to determine the baseline levels in this phase of the study. The test in which the greatest distance was covered was chosen as a reference.

The tread6MWD presented a significant inverse correlation with functional class ($r = -0.354$; $p < 0.05$), as well as a significant direct correlation with cardiac output ($r = 0.307$; $p < 0.05$) and with the 6MWD (Figure 3).

The duration of the study allowed us to analyze the survival of the study population. The evaluation of survival in function of the distance covered was performed after patients had been classified in function of the median tread6MWD (Figure 4); survival was better among the patients who covered over 377 m than among those who did not reach this cut-off value.

Of the sample as a whole (n = 73), 39 patients were included in the NO group because they had performed the acute test using a vasodi-

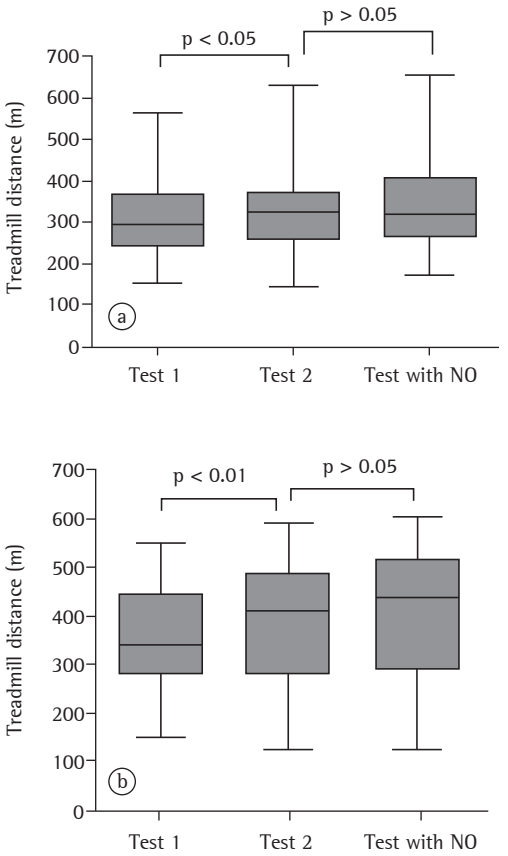

Figure 2 - Comparison between the treadmill six-minute walk distances. In a), pilot study (n = 14), with inhalation of oxygen only, via the Venturi mask. In b), the NO group (n = 39). The third test was performed with NO inhalation.

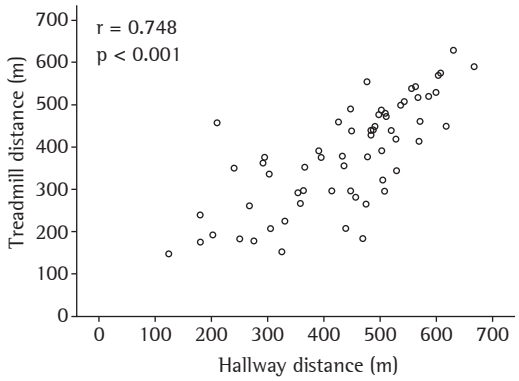

Figure 3 - Correlation between the treadmill six-minute walk distances and the hallway six-minute walk distances.

lator during right heart catheterization. Of those 39 patients, only 3 (7.7%) responded positively to NO. In this group, the third 6MWT was performed with simultaneous inhalation of NO (40 ppm). Although the mean pulmonary artery pressure, cardiac output and pulmonary vascular resistance changed with NO inhalation, the differences were not statistically significant. The same occurred with regard to the effect of NO on the tread6MWT: there was a significant difference between the first and second tread6-MWTs in terms of the tread6MWD ($p < 0.01$), confirming the findings of the preliminary phase. However, the addition of NO did not lead to a significant increase in the distance covered on the third tread6MWT ($p > 0.05$), which was analogous to what had been observed during the hemodynamic testing (Figure 2B). No significant difference was observed between responders and nonresponders (to NO during hemodynamic testing) in terms of the distance covered, although the population of responders was too small to allow us to speculate on this result.

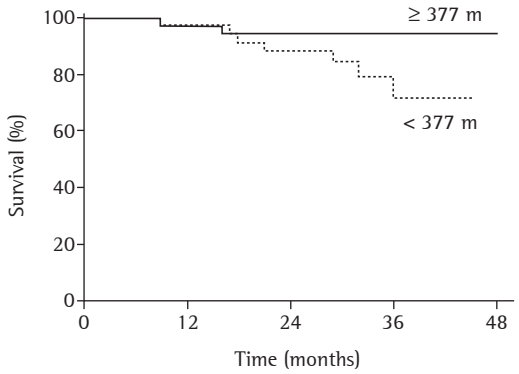

Figure 4 - Overall survival throughout the study period, according to the treadmill six-minute walk distance ($p = 0.049$, log-rank test).

Significant correlations were observed between the hemodynamic variations resulting from NO inhalation during catheterization and the variations in the tread6MWD also resulting from NO inhalation ($r = -0.370$; $p < 0.05$). Albeit weak, the positive correlation between the effect of NO on patients submitted to hemodynamic testing and the effect of NO on patients submitted to the tread6MWT suggests the potential for the protocol to be used in the evaluation of acute interventions.

Discussion

The present study was the first study to validate a protocol for the tread6MWT to evaluate PAH patients. The tread6MWT is an alternative to the functional evaluation through the act of walking in situations in which there is inadequate space or there is a need to monitor patients, or there is a combination of the two. The tread6MWT correlated with the remaining functional markers, e.g., hemodynamic markers, and was predictive of PAH patient survival. It is noteworthy that, in the present study, all patients were diagnosed using an invasive method, which ensured the diagnostic accuracy.

The demographics and hemodynamic severity of the study population were similar to those of other populations of PAH patients described in the literature,[11-13] with the exception of the subgroup of patients with schistosomiasis. This subgroup of patients was expected because of the prevalence of this disease in Brazil,[14,15] and it can explain the proportion of functional class I/II patients found in our sample. Schistosomiasis was not included in the PAH group, according to the classification of the International Symposium of Pulmonary Hypertension held in Venice in 2003, when the present study was designed. , the inclusion of schistosomiasis has always been proposed by our group and was accepted at the most recent conference (International Symposium of Pulmonary Hypertension, Dana Point, CA, USA, 2008; unpublished data).

The 6MWT is a useful and widely used tool for the evaluation of the functional capacity of patients with pulmonary or cardiac dysfunction, including PAH patients, and it can predict the

efficacy of therapeutic interventions for PAH, as well as the survival and prognosis of PAH patients.[13, 16-18] However, one of the greatest limitations of the 6MWT is that it requires adequate physical space in order to be performed, which directly affects its reproducibility.[5]

The development of a protocol for the tread6MWT aimed at creating a more readily available version of the 6MWT, to be applied especially when there are space constraints. Patients can be monitored more closely while walking on a treadmill. Although wireless telemetry systems exist, they are not widely available, which makes it difficult to monitor patients during the original 6MWT.

A previous study, also involving COPD patients walking on a treadmill,[6] provided evidence of the need to perform the tread6MWT at least twice in order to obtain a reproducible value. Similar findings have been reported regarding the hallway 6MWT, which is why it is necessary to conduct a first test in patients who have never performed the test before, i.e., to increase the reproducibility of the test.[5] Therefore, we chose to carry out the preliminary phase of our study, in which we determined that the learning curve was sharpest between the first and second tests, with a tendency toward stabilization in the third test.

The tread6MWD correlated with PAH patient functional class, one of the most widely used markers in the literature.[7,8] Therefore, the patients who presented the greatest functional limitation were those who had the worst performance in the tread6MWT, a similar finding being reported in studies involving PAH patients performing the hallway 6MWT.[3]

The hemodynamic values obtained through right heart catheterization are important because they determine disease severity and predict the treatment response and survival of PAH patients.[19,20] In the present study, the tread6MWD correlated with the hemodynamic values, particularly with cardiac output. It is of note that the degree of correlation observed between hemodynamic values and the tread6MWD in the present study is similar to that previously found for the 6MWT.[3] This shows that the hemodynamic pattern is closely related to the findings reported in studies involving walk tests with regard to the severity of PAH, despite not entirely explaining such findings.

In addition to the correlation with the functional class and hemodynamic values, the tread6MWD also correlated with the 6MWD. This shows that, like the 6MWT, the tread6MWT can measure the functional capacity of individuals by the simple act of walking. However, one test does not replace the other. The tread6MWD was shorter than the 6MWD, which was due to various factors, such as the need for coordinating upper and lower limbs in order to walk according to a speed protocol that was not established by the patient; the use of the treadmill, a device with which most of the patients included in the present study were unfamiliar; and limited maximum speed, so that the tread6MWT remained a test of submaximal effort. Therefore, the tread6MWD according to our protocol cannot be compared with the 6MWD. Both tests evaluate functional capacity in a similar, although not identical, manner.

Our study allowed us to evaluate the prognostic value of the protocol we developed for the tread6MWT. The patients who covered distances equal to or greater than the median (377 m) presented a better prognosis than did those who covered shorter distances. The interpretation of this result, however, merits special attention. The number of deaths that occurred over the course of the present study prevents us from conducting an analysis that takes into consideration all the factors potentially related to the prognosis of the study population. In addition, the medications available differed throughout the observation period, which was due to the approval of different medications by regulatory agencies, by clinical protocols and by government programs adopted in the facilities. In addition, because it was the first study in which this protocol was used, the cut-off value adopted still needs to be validated in a different group of PAH patients. However, the correlation between the distance covered and survival suggests that the protocol used in the present study can evaluate the severity of PAH.

In the present study, NO, a selective gas used in the assessment of pulmonary vasoreactivity, was used in a simple functional test that was easily performed. Therefore, we observed that, although there was no significant change in the tread6MWD with NO inhalation, there was a correlation between the variation in the tread6MWD and the hemodynamic variation

resulting from NO inhalation, i.e., the magnitude of the variation in the distance covered under the influence of NO directly correlated with the magnitude of the variation in hemodynamic values caused by the same dose of inhaled NO. This correlation suggests that the tread6MWT is capable of reflecting therapeutic interventions, at least with regard to its acute effect. It should be borne in mind that the protocol described in the present study can also reflect changes related to medium- and long-term therapeutic interventions, as previously demonstrated in studies of the 6MWT.[13,16-18]

We conclude that the tread6MWT, following the protocol described here, is useful in evaluating PAH patients because it correlates with the remaining clinical and hemodynamic markers of severity, as well as with the prognosis. The changes related to the addition of inhaled NO during the tread6MWT, although not significantly related to the baseline levels, showed a correlation with the hemodynamic changes measured during the acute test with NO inhalation, suggesting that the protocol described here is of potential use in the evaluation of pharmacological interventions.

References

1. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. N Engl J Med. 2004;351(14):1425-36.
2. Hoeper MM, Oudiz RJ, Peacock A, Tapson VF, Haworth SG, Frost AE, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. J Am Coll Cardiol. 2004;43(12 Suppl S):48S-55S.
3. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000;161(2 Pt 1):487-92.
4. Paciocco G, Martinez FJ, Bossone E, Pielsticker E, Gillespie B, Rubenfire M. Oxygen desaturation on the six-minute walk test and mortality in untreated primary pulmonary hypertension. Eur Respir J. 2001;17(4):647-52.
5. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
6. Stevens D, Elpern E, Sharma K, Szidon P, Ankin M, Kesten S. Comparison of hallway and treadmill six-minute walk tests. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1540-3.
7. Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes Brasileiras para o Manejo da Hipertensão Pulmonar. J Bras Pneumol. 2005;31(Suppl 2):S1-S31.
8. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43(12 Suppl S):5S-12S.
9. Costa EL, Jardim C, Bogossian HB, Amato MB, Carvalho CR, Souza R. Acute vasodilator test in pulmonary arterial hypertension: evaluation of two response criteria. Vascul Pharmacol. 2005;43(3):143-7.
10. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105-11.
11. Barst RJ, Langleben D, Frost A, Horn EM, Oudiz R, Shapiro S, et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2004;169(4):441-7.
12. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. N Engl J Med. 1996;334(5):296-302.
13. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896-903. Erratum in: N Engl J Med. 2002;346(16):1258.
14. Lapa MS, Ferreira EV, Jardim C, Martins Bdo C, Arakaki JS, Souza R. Clinical characteristics of pulmonary hypertension patients in two reference centers in the city of Sao Paulo [article in Portuguese]. Rev Assoc Med Bras. 2006;52(3):139-43.
15. Kloos H, Correa-Oliveira R, Oliveira Quites HF, Caetano Souza MC, Gazzinelli A. Socioeconomic studies of schistosomiasis in Brazil: a review. Acta Trop. 2008;108(2-3):194-201.
16. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med. 2005;353(20):2148-57. Erratum in: N Engl J Med. 2006;354(22):2400-1.
17. Souza R, Jardim C, Martins B, Cortopassi F, Yaksic M, Rabelo R, et al. Effect of bosentan treatment on surrogate markers in pulmonary arterial hypertension. Curr Med Res Opin. 2005;21(6):907-11.
18. Souza R, Martins BC, Jardim C, Cortopassi F, Fernandes CJ, Pulido T, et al. Effect of sitaxsentan treatment on quality of life in pulmonary arterial hypertension. Int J Clin Pract. 2007;61(1):153-6.
19. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115(5):343-9.
20. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002;40(4):780-8.

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