Functional evaluation of patients with chronic pulmonary hypertension

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The importance of studying the pathophysiological bases and clinical correlates of exercise limitation in patients with pulmonary arterial hypertension (PAH) is well established. Two modes of exercise testing, the 6-min walk test (6MWT) and the cardiopulmonary exercise test (CPET), are currently proposed for diagnostic, therapeutic and prognostic finalities.

The 6MWT is inexpensive, feasible and is thought to better reproduce daily life activities and to reliably detect therapeutic benefits. CPET requires the patient's maximal effort and does not provide a reliable quality of life measure. It is, however, highly reproducible and provides remarkable insights into the pathophysiological mechanisms that lead to exercise intolerance. Due to the limited experience accumulated, CPET is not actually advised for the routine assessment and for the overall clinical decision making of PAH patients.

In this review we critically address the knowledge currently acquired on these techniques.
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Impaired physical performance is an important hallmark of patients with pulmonary arterial hypertension (PAH). Since the extent of functional limitation fairly reproduces the disease severity and risk rate, the acquisition of objective measures of exercise capacity is warranted. Scientific evidence basically relies on the information provided by two different exercise modalities, i.e. the 6-min walk test (6MWT) and the cardiopulmonary exercise test (CPET). The following subheadings provide an outlook for the clinical investigator on how and whether these tests may be helpful and complementary in the assessment of this specific disorder.

Six-minute walking test

The 6MWT has been considered to realistically reflect activities of daily living. Consequently, it has been incorporated into studies of assessment of exercise capacity, quality of life, efficacy of new therapeutic agents and prognostic stratification in PAH patients. The 6MWT is technically simple, does not require expensive equipment or advanced training for technicians, is easy to interpret. The American Thoracic Society published specific guidelines for the test[1].

The reproducibility of the walked distance measured is weak. Shorter legs, older age, higher body weight, female gender, impaired cognition, muscle wasting, comorbid conditions (i.e. cardiac disease, arthritis) could be associated with shorter 6MWT distance, independently of the severity of the PAH disease. Encouragement and enthusiasm of the technician can make a difference of up to 30% in the 6MWT distance[2]. A learning effect is clear and may be due to improved coordination, finding optimal stride length and overcoming anxiety[3]. If oxygen supplementation is needed, the type of oxygen delivery device and flow should be noted in order to be taken into account during following tests.

The distance walked in 6 min is the parameter usually taken into consideration and it could be expressed as an absolute value (one-time measure) or a percentage of the predicted value (taking into account anthropometric variables)[4], and an absolute or a percentage change (for example in the same patient when evaluating the effects of a treatment). During the test some other parameters could be monitored, such as the number of times the patient has to stop, the walking speed of walking, the Borg score of dyspnea and fatigue[5], the arterial oxygen saturation (SaO_2) (by a pulse oximeter), the respiratory rate and gases (by a portable instrument), and the amount of supplemental oxygen used during the test.

Six-min walk test value in the clinical and prognostic evaluation. Distance walked in 6MWT is significantly shorter in PAH patients than in age- and sex-matched healthy subjects[6]. The relation of the 6MWT results and etiology of PAH is not completely known[7]. The test has been used in sclerodermia-associated PAH[8] and in the Eisenmenger syndrome[9], but not in portopulmonary hypertension patients. The distance significantly decreases in proportion to the severity of NYHA/WHO functional class[6]. The 6MWT results weakly correlate with resting hemodynamic variables[10]. Moreover, it seems to be inversely correlated with B-type natriuretic peptide levels, suggesting that these two parameters together may better describe the severity of the disease[10]. The 6MWT is usually considered a submaximal exercise but in moderate-to-severe patients the results correlate with peak oxygen consumption (VO_2), oxygen pulse and minute ventilation/carbon dioxide output (VE/VCO_2) slope determined by cardiopulmonary exercise testing[6]. Therefore, in some cases the 6MWT may reflect maximal exercise tolerance. The test has been proposed as a measure of health-related quality of life. Compared with normal people, PAH patients report moderate-to-severe impairment in multiple domains of health-related quality of life, including physical mobility, emotional reaction, pain, energy, sleep, and social isolation[11], but, to the best of our knowledge, any significant correlation with the 6MWT distance has never been found. Moreover, therapy, such as intravenous epoprostenol[11] or sitaxsentan[12], showed an improvement in 6MWT distance, but no differences in quality-of-life assessment. In summary, the real additional informative contribution of the test with respect to the standard clinical (NYHA/WHO classification) and functional indicators (CPET) has not been completely clarified.

After PAH diagnosis, disease severity should be assessed in order to accurately determine risk and benefit profiles for various therapeutic options. Useful tools to predict outcome include, among others, functional class and exercise capacity. A relatively low walked distance (< 400 m) appeared to be a reasonable prognostic marker in some retrospective chart reviews of patients assessed for lung transplant (Toronto Lung Transplant Program[13] and Swiss Registry[14]). However, there is not real evidence that the 6MWT distance had a real prognostic contributory power, above the standard clinical and functional indicators. Few reports focused on the independent prognostic power of the 6MWT. Only two[6,15] provided positive results, evaluating relative few patients. In the multivariate analysis of the Miyamoto study[6] on 43 primary PAH (PPAH) patients followed for a mean of 21 months (12 deaths), among non-invasive parameters including clinical, echocardiographic, and neurohumoral parameters, the distance walked in 6MWT was independently related to mortality; patients walking < 332 m had a significantly lower survival rate than those walking farther. In the other study by Barst et al.[15], the performance at the 6MWT was found at the multivariate analysis to be an independent predictor of survival, being significantly lower in the 8 patients who died (in all of them was < 150 m) vs the 73 survivors (mean 305 m). In this study, however, the treatment varied between survivors and non-survivors limiting interpretation of these findings. In other studies the distance walked was associated with survival at univariate analysis but did not reach statistical significance as an independent predictor of survival by multivariate analysis[16,17]. In some trials, finally, only univariate analysis was performed and redundancy of the 6MWT variable could not be excluded[18].

In addition, the 6MWT has not been validated as an endpoint in patients with less severe disease (NYHA/WHO functional class I and II)[19]. The prognostic power of a reduction of SaO_2 during walking test was studied and confirmed by Paciocco et al.[20]. The authors found that not the 6MWT distance walked but a reduction of > 10% in SaO_2 increased mortality risk by 2.9 times. However, it should be noticed that in Paciocco's protocol, the test should be stopped if SaO_2 decreased to < 86%: this could have limited the effective practicable distance. Finally, the 6MWT distance response to therapy has been studied as a prognostic indicator. But, again, there is not a strong evidence-based conclusion. For instance, in a study on 178 patients in NYHA functional class III or IV treated with epoprostenol, the treatment distance walked improved at 3 months with a mean increase of 147 m. However, on multivariate analysis including both baseline variables and those measured after 3 months on epoprostenol, a history of right-sided heart failure, persistence of NYHA functional class III or IV at 3 months, and the absence of a fall in total pulmonary resistance of > 30% relative to baseline were associated with poor survival, but the change in distance walked was not a predictor of survival[17].

In summary, there is no strong evidence that walking performance provides independent prognostic information which can either complement or substitute that provided by other variables. Anyway, in the recently published evidence-based clinical practice recommendations[21], a low 6MWT distance is defined as a "possible useful" predictor of worse prognosis and, to date, the 6MWT is the only measure of exercise capacity that has been accepted by the Food and Drug Administration, based on its validation as a marker of treatment efficacy.

To date, the majority of the randomized controlled clinical trials performed in PAH have been relatively short-term (12 weeks) studies performed for the purpose of drug registration. Nearly all of these trials have used exercise capacity, measured by the 6MWT, as the primary endpoint. This approach has been productive, leading to the licensing of a number of effective treatments[22]. However, as a consequence of the wide vari-

ability of the test, the clinical relevance of the results of intervention studies must be considered cautiously if the variation in the distance is < 10% in individuals. Small differences may be statistically significant but not clinically significant (i.e. as seen in the Olschewski's experience by inhaled iloprost[23]). Regulatory agencies are currently accepting the 6MWT as a primary endpoint for PAH trials, but with a "given improvement" in the distance walked defined *a priori* in the protocol of the study. Redelmeier et al.[24] advice to include the awareness of the difference in walking distance noticeable to patients to help clinicians interpret the effectiveness of symptom treatments. A consistent placebo effect, that is a mean overall improvement in functional capacity, was observed in almost all pharmacological trials in the first exercise test performed after baseline values (usually after 4-6 weeks). In near all pharmacological trials, in fact, the walking capacity improved after treatment (treatment effect ranging form a mean difference of 16 to 76 m). Even when additional parameters such as morbidity, mortality, rescue therapies, quality of life and hemodynamics are taken into consideration the question about the clinically meaningfulness of the increase in the distance walked remains difficult to answer. Some treatments (i.e. treprostinil) achieved a low treatment effect on walking capacity but reduced combined clinical events and improved symptoms score, hemodynamics and physical dimension of quality of life[25]. On the contrary, a high increase in the 6MWT distance was obtained by bosentan studies, together with an improvement in NYHA class and hemodynamics and a reduction in clinical events[18,26,27].

In summary, among the primary endpoints currently accepted by the regulatory agencies[19,28], exercise capacity at the 6MWT, as well as quality of life and time to clinical worsening (death, hospitalizations due to worsening, escalation of treatments) require careful standardization, validation and still arise some concerns.

Conclusions. The 6MWT has advantages, like ability to assess a global and integrated response of systems required for daily functioning, simplicity of performance, inexpensiveness, but also weakness as variability, limited clinical informative content, unproven independent prognostic power. This prevents firm conclusions being reached on the usefulness of the test as a decisional indicator in clinical practice in PAH patients.

Cardiopulmonary exercise testing

Exercise is the ideal physiological condition for the investigation of the integrated response of the cardiopulmonary system and the functional gas exchange evaluation by CPET is considered the gold standard for its assessment. Although functional evaluation by CPET may still be viewed as a complex and poorly feasible technique, there is now consistent evidence on the amount of pathophysiological, clinical and prognostic information provided by this technique in most cardiopulmonary disorders[29,30]. In patients with PPAH, CPET has been only recently gaining a role in the clarification of the complex pathophysiology of exercise intolerance[31,32], in the assessment of therapeutic effectiveness of modern approaches[33,34] and in the definition of prognostic correlates[35].

Pathophysiological insights. PPAH patients exhibit an exercise gas exchange analysis profile similar to that observed in heart failure patients with secondary PAH as documented by a reduced peak VO_2, work rate, ratio of VO_2/work rate increase, peak oxygen pulse, tidal volume, end-tidal of carbon dioxide (CO_2) and by an increased dead space ventilation and VE/VCO_2 slope (Fig. 1). However, the pathophysiological bases are quite different. On exertion, these patients typically exhibit an increased ventilatory requirement and experience dyspnea sensation for low levels of exercise. The underlying pathophysiology consists of an intrinsic abnormality of the pulmonary vasculature resulting in intimal fibrosis, medial hypertrophy and formation of plexiform lesions. These changes lead to an increased vascular resistance and failure to perfuse ventilated lung tissue. The two most important functional correlates are the occurrence of ventilation/perfusion mismatching with an increased dead space ventilation and oxygen failure to be appropriately delivered to working muscles because the increase in pulmonary blood flow and cardiac output is limited. The reason for an inadequate oxygen transport is that the right ventricle fails to overcome the increased pulmonary vascular resistance in order to increase pulmonary blood flow. This yields to left ventricular underfilling, with a resultant decrease in stroke volume, which is also induced by the compression of the enlarged right ventricle against the left one. In the presence of inadequate oxygen delivery, anaerobic metabolism ensues to enhance the energy supply for incrementing exercise. The increase in CO_2 production relative to VO_2 due to bicarbonate dissociation for lactic acid tamponade provides a further stimulus to the ventilatory drive as detected by an increased VE/VCO_2 slope[30,32]. While there is clear documentation that an increased dead space and a premature lactic acidosis are involved in the elevated exercise VE/VCO_2 slope, the potential role of an impaired peripheral reflexogenic control from muscular fibers (i.e. ergoreflex) has not been tested.

In a significant percentage of PPAH cases there is a typical right-to-left shunt through the patent foramen ovale whose CPET highly sensitive diagnostic correlates are an abrupt decrease of end-tidal CO_2 pressure and an increase in the respiratory exchange ratio and in the ventilatory requirement for CO_2[32].

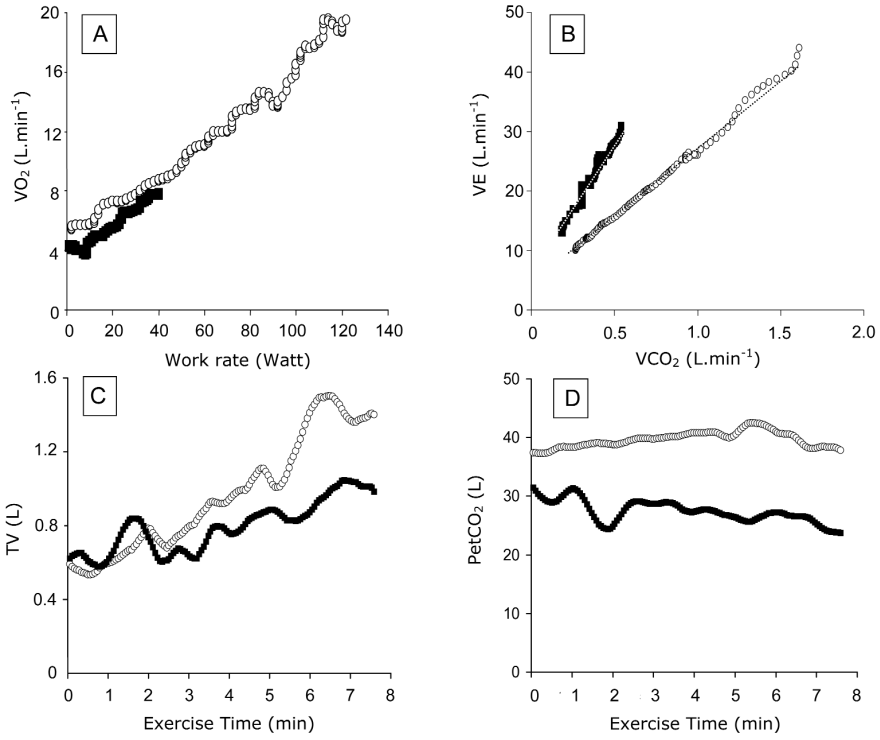

Figure 1. *Cardiopulmonary exercise test-derived variables recorded in one moderate primary pulmonary arterial hypertension female patient (40 years old) and one age- and sex-matched healthy control. Protocol consisted of a personalized linear ramp maximal test with a work rate increase of 5 W/min for the primary pulmonary arterial hypertension patient and of 15 W/min for the control subject. Accordingly, exercise duration was approximately 8 min for both tests.* A: *changes in oxygen consumption (VO_2) vs changes in work rate.* B: *relationship of the increase in minute ventilation (VE) vs carbon dioxide output (VCO_2).* C: *tidal volume (TV).* D: *end-tidal of carbon dioxide ($PetCO_2$).*

Cardiopulmonary exercise test value in the clinical and prognostic evaluation. Although CPET provides the most comprehensive approach for studying the pathophysiological correlates of exercise limitation in PPAH patients, the present consensus is that it is not advantageous compared to other types of exercise testing in the long-term management of these patients[21,36]. The American Thoracic Society/American College of Chest Physicians guidelines warn on the risks of performing a maximal CPET in patients with severe forms of pulmonary vascular diseases[37], but the paucity of studies performed and the difficulties related to compare results obtained in different laboratories appear the main reasons for not advising CPET as a routine test. Lack of correlation with the daily activity[21,36], impossibility for patients with severe PPAH of exercising at their maximum[6,38] and failure to detect pharmacological improvements observed with 6MWT[39,40] are additional common criticisms moved to this technique even though the test is highly reproducible independently of exercise limitation severity[41]. Sun et al.[31] interestingly documented the potential for CPET of non-invasively grading the severity of exercise limitation before overt right ventricular failure and PAH are evident at rest. If confirmed by other studies, CPET could be proposed as a screening test in the initial stages of the disease when clinical suspicious of developing PPAH is present.

At least theoretically, monitoring gas exchange analysis at low-intensity constant workloads appears the best modality for testing these patients mainly considering the above discussed basic conceptual limitations regarding 6MWT[1,6]. In this regard, measuring gas exchange VO_2 kinetics during a constant exercise at low workload would have the advantage of clearly defining the "aerobic nature" of exercise without stressing patients to their higher performance. This approach that provides valuable clinical and prognostic information in patients with heart failure[42,43] has never been performed in PPAH patients and should be pursued in upcoming trials.

Information regarding the prognostic ability of CPET-derived variables in PPAH patients are limited. Wensel et al.[35] prospectively investigated the prognostic power of CPET-derived variables in a PPAH population of 86 patients. In this isolated study the strongest predictors of impaired survival were low peak VO_2 and low systolic blood pressure at peak exercise. More recently, Yetman et al.[44] looked at the CPET response in a population exclusively composed by children with PPAH, showing that a significant reduction in maximal performance may be documented since younger ages and percent predicted VO_2 is discriminatory for adverse events. In contrast with the compelling evidence coming form studies performed in heart failure patients

with secondary PAH, powered PPAH studies investigating the relative prognostic significance of VE/VCO_2 slope are lacking. This would provide a step forward in the recognition of those CPET variables that track the natural history and grade the severity of the disease.

Presently, there is limited experience with the use of CPET in multicenter pharmacological trials and the interpretation of the results of the test is influenced by the level of experience. For this reason, the Endpoint Task Force members did not recommend CPET as a primary endpoint in multicenter trials on new treatments in PAH; however, the use of CPET in substudies involving centers with experience in CPET is stimulated in order to generate secondary endpoints in forthcoming studies[19].

Conclusions. In PPAH, CPET definitively contributes to the identification of pathophysiological mechanisms underlying exercise intolerance. The limited experience gained with this exercise testing modality seems, at the moment, to preclude definitive conclusions on the overall CPET validity in the clinical and prognostic assessment of this disease.

References

1. 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: 111-7.
2. Enright PL. The six-minute walk test. Respir Care 2003; 48: 783-5.
3. Opasich C, Pinna GD, Mazza A, et al. Reproducibility of the six-minute walking test in patients with chronic congestive heart failure: practical implications. Am J Cardiol 1998; 81: 1497-500.
4. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998; 158: 1384-7.
5. Borg GA. Psycho-physical bases of perceived exertion. Med Sci Sports Exerc 1982; 14: 377-81.
6. Miyamoto S, Nagaya N, Satoh T, 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 (Part 1): 487-92.
7. Sztrymf B, Francoual J, Sitbon O, et al. Clinical, haemodynamic and genetic features of familial pulmonary arterial hypertension. Rev Mal Respir 2004; 21: 909-15.
8. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000; 132: 425-34.
9. Sandoval J, Aguirre JS, Pulido T, et al. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med 2001; 164: 1682-7.
10. Leuchte HH, Holzapfel M, Baumgartner RA, et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. J Am Coll Cardiol 2004; 43: 764-70.
11. Shafazand S, Goldstein MK, Doyle RL, Hlatky MA, Gould MK. Health-related quality of life in patients with pulmonary arterial hypertension Chest 2004; 126: 1452-9.
12. Barst RJ, Langleben D, Frost A, et al, for the STRIDE-1 Study Group. Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169: 441-7.
13. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. J Heart Lung Transplant 1997; 16: 313-9.
14. Stricker H, Domenighetti G, Popov W, et al, on behalf of the Swiss Group for Severe Pulmonary Hypertension. Severe pulmonary hypertension: data from the Swiss Registry. Swiss Med Wkly 2001; 131: 346-50.
15. Barst RJ, Rubin LJ, Long WA, 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: 296-302.
16. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 2002; 39: 1214-9.
17. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002; 40: 780-8.
18. McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 2005; 25: 244-9.
19. Hoeper MM, Oudiz RJ, Peacock A, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. J Am Coll Cardiol 2004; 43 (Suppl): 48S-55S.
20. 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: 647-52.
21. McLaughlin VV, Presberg KW, Doyle RL, et al, for the American College of Chest Physicians. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines Chest 2004; 126 (Suppl): 78S-92S.
22. Peacock A, Naeije R, Galie N, Reeves JT. End points in pulmonary arterial hypertension: the way forward. Eur Respir J 2004; 23: 947-53.
23. Olschewski H, Simonneau G, Galie N, et al, for the Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension N Engl J Med 2002; 347: 322-9.
24. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997; 155: 1278-82.
25. Simonneau G, Barst RJ, Galie N, et al, for the Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 2002; 165: 800-4.
26. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346: 896-903.
27. Sitbon O, Badesch DB, Channick RN, et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: a 1-year follow-up study. Chest 2003; 124: 247-54.
28. Kawut SM, Palevsky HI. Surrogate end points for pulmonary arterial hypertension. Am Heart J 2004; 148: 559-65.
29. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation. Malvern, PA: Lea & Febiger, 1994.

30. Guazzi M. Exercise testing to monitor heart failure treatment. In: Wasserman K, ed. Cardiopulmonary exercise testing and cardiovascular health. Armonk, NY: Futura Publishing Company, 2002: 221-38.
31. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001; 104: 429-35.
32. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. Circulation 2002; 105: 54-60.
33. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. Circulation 2000; 101: 2388-92.
34. Nagaya N, Kyotani S, Uematsu M, et al. Effects of adrenomedullin inhalation on hemodynamics and exercise capacity in patients with idiopathic pulmonary arterial hypertension. Circulation 2004; 109: 351-6.
35. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002; 106: 319-24.
36. Hoeper MM, Oudiz RJ, Peacock A, et al. End points and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43 (Suppl): 48S-55S.
37. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211-77.
38. Rhodes J, Barst RJ, Garofano RP, Thoele DG, Gersony WM. Hemodynamic correlates of exercise function in patients with primary pulmonary hypertension. J Am Coll Cardiol 1991; 18: 1738-44.
39. Barst RJ, McGoon M, Laughlin VV, et al. Beraprost therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2003; 41: 2115-25.
40. Barst RJ, Langleben D, Frost A, et al. Sitaxsetan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 2004; 169: 441-7.
41. Hansen JE, Sun XG, Yasunobu Y, et al. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. Chest 2004; 126: 816-24.
42. Koike A, Yajima T, Adachi H, et al. Evaluation of exercise capacity using submaximal exercise at a constant work rate in patients with cardiovascular disease. Circulation 1995; 91: 1719-24.
43. Guazzi M, Agostoni PG. Monitoring gas exchange during a constant work rate exercise in patients with left ventricular dysfunction treated with carvedilol. Am J Cardiol 2000; 85: 660-4.
44. Yetman AT, Taylor AL, Doran A, Dunbar Ivy D. Utility of cardiopulmonary stress testing in assessing disease severity in children with pulmonary arterial hypertension. Am J Cardiol 2005; 95: 697-9.