Initial Diagnostic Testing in the Evaluation of Pulmonary Hypertension

Terence K. Trow, MD
Director, Pulmonary Hypertension Center
Assistant Professor of Medicine
Yale University School of Medicine
New Haven, Connecticut

Terence K. Trow, MD

Diagnosing pulmonary arterial hypertension (PAH) requires a high index of clinical suspicion from even the most astute clinician, especially given the lack of specificity of the symptoms offered by the PAH patient. In addition, even mild elevations in pulmonary arterial pressure may represent fairly advanced pulmonary vascular disease making early detection difficult.[1] As discussed by Dr Bull in the accompanying article, many clues from the history and physical may prompt further testing. In this segment, the noninvasive methods available to pursue a diagnosis of PAH will be reviewed.

The Electrocardiogram

While electrocardiography lacks sufficient sensitivity to serve as an effective screening tool for PAH, it can contribute important prognostic information and should be performed.[1] Right ventricular hypertrophy and right-axis deviation can be detected 87% and 79% of the time in PAH.[2] Findings suggestive of PAH include a tall R wave and small S wave (R/S ratio greater than 1) in lead V_1, a large S wave and small R wave (R/S ratio less than 1) in lead V_5 or V_6, a qR complex in V_1, an rSR' pattern in lead V_1, or an $S_1S_2S_3$ pattern. Right atrial enlargement should also be looked for, defined as a tall P wave in lead II, III, and aVF (greater than 2.5 mm) and a frontal P axis of 75 or greater. However, the absence of these findings does not exclude a diagnosis of PAH, with one study of 61 patients with PAH showing 8 with normal electrocardiograms despite severe PAH, and sensitivities of 73% for right-axis deviation and 55% for right ventricular hypertrophy noted.[3] Specificity was only 70% in that population as well.[3] The ECG may be helpful prognostically, independent of its role in diagnosis, in patients with established PAH since the presence of right atrial enlargement (P wave 0.25 millivolts or greater) has been associated with a 2.8-fold greater risk of death over a 6-year period of observation.[4] The presence of electrocardiographic findings of right atrial enlargement, right ventricular hypertrophy, and right-axis deviation should prompt further evaluation in the patient with suspected PAH.

Chest Radiography

Like the electrocardiogram, a chest radiograph should be obtained in all patients with suspected PAH even though it lacks sensitivity and specificity to establish a diagnosis. Suggestive clues that should be sought include attenuated peripheral markings, enlarged main and hilar pulmonary artery shadows, and obscuration of the retrosternal clear space on a lateral view due to an enlarged right ventricle. Lupi et al described a radiologic index in PAH defined as the ratio of the summed horizontal measurement of the pulmonary arteries from the midline to their first division divided by the entire transverse chest diameter.[5] The chest radiograph may also define concomitant pulmonary parenchymal disease, pulmonary venous congestion (seen in pulmonary veno-occlusive disease), hyperinflation changes of chronic obstructive pulmonary disease (COPD), kyphosis, or findings suggestive of chronic thromboembolic pulmonary hypertension (CTEPH) such as mosaic oligemia, right ventricular hypertrophy, or an enlarged descending right pulmonary artery.[6] The extent of radiographic abnormalities and the degree of PAH in any given patient do not appear to be correlated.[1]

Transthoracic Echocardiography

The reliability of Doppler echocardiography to quantify PAH has been extensively studied. While numerous studies report excellent correlation coefficients as a measure of accuracy, technical aspects of interrogation make tricuspid regurgitant jets (a requisite feature of systolic pulmonary arterial pressure estimates by the modified Bernoulli equation) analyzable in anywhere from 39%[7] to 86%[8] of patients. Patients with advanced lung disease may represent a challenge as estimates of systolic pulmonary arterial pressure were achievable in only 44% of 166 such patients in one study.[9] When tricuspid and pulmonic valve regurgitant jets are not present or quantifiable, estimates of pulmonary diastolic pressures may be useful[10] and these correlate well with right-heart catheterization measures.[11] While correlations are generally strong with catheterization data the magnitude of difference between estimated and true pulmonary arterial pressure as measured by right-heart catheterization can be significant, with mean differences ranging from 3 to 38 mm Hg.[1] Discordance is generally greatest at extremes, with

underestimation common when systolic pulmonary arterial pressure is greater than 100 mm Hg.[12] Advanced lung disease patients pose a special challenge, with 48% of patients misclassified as having PAH and 52% of pressure estimates inaccurate in a cohort of 374 patients being assessed for lung transplantation.[9] Despite these caveats, the sensitivity and specificity of Doppler echocardiography range from 0.79 to 1.0 and 0.6 to 0.98, respectively.[13-16]

The role of exercise echocardiographic testing to unmask PAH remains controversial. One study examined the features of the resting echocardiogram (with normal resting systolic pulmonary arterial pressure) in those with exercise-induced PAH and found that tricuspid regurgitation and right ventricular outflow velocity time integral at peak velocity distinguished exercise PAH from normal PAH.[16] Interestingly, recent studies of idiopathic pulmonary hypertension (IPAH) family members suggest that supine bicycle exercise echocardiography may identify a subgroup of asymptomatic carriers of the PAH gene.[17,18]

Since false-positive testing is more common when the prevalence of disease is low, focused ordering of Doppler echocardiography in an asymptomatic population at risk is advisable,[1] as overestimation of systolic pulmonary arterial pressure is more likely in populations with normal pressures.[15,19] Risk factors that warrant screening echocardiography include known genetic mutations associated with PAH, a first degree relative with familial PAH (FPAH), a diagnosis of scleroderma, portal hypertension prior to liver transplantation, or congenital heart disease with systemic-to-pulmonary shunts.[1] When PAH is suspected or estimated by Doppler echocardiography, a contrast "bubble" echocardiogram should be obtained to assess for left-to-right shunting.[1] In addition, left atrial enlargement, even in the absence of left ventricular dysfunction, should raise the possibility of elevated left-sided pressures that may be contributing to the pulmonary pressure elevation seen. When present, right-heart catheterization, and often left-heart catheterization, to measure transpulmonary gradient and to assess for diastolic dysfunction is crucial.[1]

Serologic Testing

In order to define PAH association with certain connective tissue disease, a serologic assessment should be performed in conjunction with features of the individual patient's history and exam findings. Since the most common connective tissue disease associated with PAH, limited scleroderma, typically will not manifest interstitial disease on exam or chest radiography, patients with perceived IPAH should be carefully assessed for features of systemic sclerosis. Estimates of PAH prevalence in scleroderma range from 4.9%[20] to 38%.[21] When PAH is present in association with diffuse scleroderma, U3-RNP antibodies are often positive.[22] When PAH develops in those with limited scleroderma it usually does so slowly[1] and in association with 1) positive anticentromere antibodies,[23] 2) positive antinuclear antibodies including U3-RNP, B23, Th/To, and U1-RNP,[24-26] and 3) marked reductions in diffusing capacity for carbon monoxide (DLCO) on pulmonary function testing.[13,27] In fact, 20% of those with limited scleroderma and isolated carbon monoxide diffusing capacity reductions of less than 55% of predicted values will acquire PAH within 5 years.[28]

Other connective tissue diseases such as systemic lupus erythematosis, polymyositis, and rheumatoid arthritis are less commonly associated with PAH.[29,30] In mixed connective tissue disease, however, one study found that PAH was the most common cause of death, occurring in 38% of these patients.[31] Anticardiolipin antibodies have been associated with PAH in at least two studies of systemic lupus erythematosis patients.[32,33] Human immunodeficiency virus (HIV) is associated with PAH in up to 0.5% of HIV infections,[34] and HIV testing is advised in all appropriate cases of unexplained PAH.[1] Evaluation for liver disease is also appropriate as 2% of these patients have been found to have PAH in one study.[35] Thyroid function abnormalities have also been suggested as a risk factor for PAH, although it is unclear at present whether thyroid disease is causally related to PAH.[1]

Excluding Thromboembolic Disease

Since PAH develops as a complication of chronic thromboembolic disease (CTEPH) and can mimic IPAH, this potentially surgically remediable entity should be looked for in all patients with PAH.[1] Indeed, one recent study concluded that CTEPH occurs in up to 4% of patients surviving their pulmonary embolism, usually within 2 years of the event.[36] Ventilation-perfusion (V/Q) scanning is the screening method of choice, typically showing one or more segmental-sized mismatched defects.[37] A normal V/Q scan effectively rules out CTEPH.[38,39] Perfusion scans alone tend to underestimate the severity of vessel obstruction in CTEPH.[40] While both contrast-enhanced computerized tomography and magnetic resonance imaging have utility in defining alternative diagnoses (eg, sarcoma, vasculitis, mediastinal fibrosis) and may be complementary to V/Q scanning, these techniques should not be used to exclude the diagnosis of CTEPH.[1] Pulmonary angiography is ultimately required for accurate diagnosis and anatomic definition of CTEPH and remains the procedure of choice.[1]

Pulmonary Function Testing

Pulmonary function testing is an important adjunct in the initial evaluation of all patients with PAH. Restrictive defects are not uncommon in IPAH and CTEPH patients, with 20% demonstrating such defects at initial evaluation,[2,37] and mild diffusing capacity for carbon monoxide impairment is likewise often observed in these patients.[41] Isolated abnormalities in carbon monoxide diffusing capacity occur in limited scleroderma[13,27] and, in fact, when severe (less than 55% of predicted), 35% of these patients will acquire demonstrable PAH within 5 years.[28] A fall in the carbon monoxide diffusing capacity values is suggestive of early development of PAH.[28] A widened alveolar-arterial oxygen gradient may also be suggestive of IPAH and CTEPH.[38] Desaturation during exercise occurs in all forms of PAH because of the inability of the failing right ventricle to increase cardiac output adequately.[1] Nocturnal oxygen desaturation, even in the absence of sleep-disordered breathing, is surprisingly common in PAH, occurring in up to 75% of IPAH patients.[42]

Magnetic Resonance Imaging

Exquisite experimental work using MRI evaluation of right ventricular dysfunction in PAH has begun to appear in the literature,[43,44] with some authors proposing it may be superior to echocardiography in estimating pulmonary arterial pressure.[44] In CTEPH, one report suggested that good correlation to V/Q results can be expected with MRI in experienced hands.[45,46] Noninvasive measures of right ventricular chamber size,[20] shape, thickness, and mass can also be offered by MRI,[47] and mean pulmonary arterial pressure has been shown to correlate with MRI measurement of right ventricular thickness, main pulmonary artery diameter,[48] and right ventricular mass.[49] Nonetheless, the incremental clinical value of MRI and computed tomographic techniques to traditional echocardiographic assessments in PAH have not been reported.[1]

Exercise Testing

Measures of exercise intolerance may be helpful in diagnosing early PAH (before it is present at rest) as well as in predicting survival and response to therapy.[50,51] Because PAH patients are limited in the extent to which they are able to raise cardiac output in response to tissue oxygen demands, small increases in workload can result in significant hypoxemia. Reductions in maximum peak oxygen consumption ($VO_{2\ max}$), anaerobic threshold, peak O_2 pulse, rate of increase in VO_2, and ventilatory efficiency as assessed by cycle ergometry cardiopulmonary exercise testing correlate well with New York Heart Association functional class.[52] In addition end-tidal partial pressure of carbon monoxide (P_{ETCO2}) in IPAH patients is significantly reduced at rest and exercise in proportion to physiologic disease severity, and this finding on cardiopulmonary exercise testing when accompanied by arterial hypoxemia should trigger consideration of pulmonary vasculopathy.[53] Cardiopulmonary exercise testing has been found reproducible and safe without complications or fatalities in even the most severely exercise-intolerant PAH patient.[54] Peak VO_2 and peak systolic blood pressure during cardiopulmonary exercise testing have also been shown to independently predict survival in PAH patients.[55] Peak VO_2 measures and ventilatory efficiency by cardiopulmonary exercise testing also show progressive improvement in response to surgical thromboendarterectomy in CTEPH.[56]

A simple and practical substitute for full cardiopulmonary exercise testing is the 6-minute walk test. This validated test shows strong correlation between the distance ambulated and peak VO_2 seen on cardiopulmonary exercise testing,[57] as well as to total pulmonary vascular resistance, mean right atrial pressure, baseline cardiac output, and New York Heart Association functional class.[58] The 6-minute walk test can also predict disease progression and patient's response to therapy[59] and is commonly used for this purpose clinically.

Summary

While right-heart catheterization is ultimately required, a constellation of noninvasive tests exist to aid the clinician in consolidating his or her diagnosis of PAH. These include the electrocardiography, chest radiography, pulmonary function tests, nocturnal oximetry, blood serologies, computed tomography, Doppler echocardiography with and without "bubble" contrast, and cardiopulmonary exercise testing. While none of these taken in isolation are adequate to definitively establish the diagnosis, when assessed in combination these tests are most helpful in defining who should proceed to right-heart catheterization. All patients with unexplained PAH should undergo V/Q scanning to avoid missing surgically remediable CTEPH. While magnetic resonance imaging and contrast-enhanced computed tomographic angiography can be complimentary, pulmonary angiography remains the procedure of choice to define operability when CTEPH is uncovered.

References

1. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126:14S-34S.
2. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med.* 1987;107:216-23.
3. Ahern GS, Tapson VF, Rebeiz A, et al. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. *Chest.* 2002;122:524-7.
4. Bossone E, Paciocco G, Iarussi D, et al. The prognostic role of the ECG in primary pulmonary hypertension. *Chest.* 2002;121:513-8.
5. Lupi E, Dumont C, Tejada VM, et al. A radiologic index of pulmonary hypertension. *Chest.* 1975;68:28-31.
6. Woodruff WW III, Hoeck BE, Chitwood WR Jr, et al. Radiographic findings in pulmonary hypertension from unresolved embolism. *AJR Am J Roentgenol.* 1985;144:681-6.
7. Murata I, Kihara H, Shinohara S, et al. Echocardiographic evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. *Jpn Circ J.* 1992;56:983-91.
8. Borgeson DD, Seward JB, Miller FA Jr, et al. Frequency Doppler measurable pulmonary artery pressures. *J Am Soc Echocardiogr.* 1996; 9:832-7.
9. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med.* 2003;735-40.
10. McGoon MD, Fuster V, Freeman WK, et al. The heart and lungs: pulmonary hypertension. In: Guiliani ER, Gersh BJ, Holmes DR, et al, eds. *Mosby Yearbook.* New York, NY: Mosby; 1996:1815-36.
11. Stephen B, Dalal P, Berger M, et al. Noninvasive estimation of pulmonary artery diastolic pressure in patients with tricuspid regurgitation by Doppler echocardiography. *Chest.* 1999;116:73-7.
12. Brecker SJ, Gibbs JS, Fox KM, et al. Comparison of Doppler derived haemodynamic variables and simultaneous high fidelity measurements in severe pulmonary hypertension. *Br Heart J.* 1994;72:384-9.
13. Denton CP, Cailes JB, Phillips GD, et al. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Br J Rheumatol.* 1997;36:239-43.
14. Kim WR, Krowka MJ, Plevak DJ, et al. Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. *Liver Transpl.* 2000;6:453-8.
15. Penning S, Robinson KD, Major CA, et al. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. *Am J Obstet Gynecol.* 2001;184:1568-70.
16. Bossone E, Avelar E, Bach DS, et al. Diagnostic value of resting tricuspid regurgitation velocity and right ventricular ejection flow parameters for the detection of exercise induced pulmonary arterial hypertension. *Int J Card Imaging.* 2000;16:429-36.
17. Gruenig E, Janssen B, Mereles D, et al. Abnormal pulmonary artery pressure response in asymptomatic carriers of primary pulmonary hypertension gene. *Circulation.* 2000;102:1145-50.

18. Rindermann M, Grunig E, von Hippel A, et al. Primary pulmonary hypertension maybe a heterogeneous disease with a second locus on chromosome 2q31. *J Am Coll Cardiol.* 2003;41:2237-44.
19. Naeije R, Torbicki A. More on the noninvasive diagnosis of pulmonary hypertension: Doppler echocardiography revisited. *Eur Respir J.* 1995;8:1445-9.
20. Koh ET, Lee P, Gladman DD, et al. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol.* 1996;35:989-93.
21. Rolla G, Colagrande P, Scappaticci E, et al. Exhaled nitric oxide in systemic sclerosis: relationships with lung involvement and pulmonary hypertension. *J Rheumatol.* 2000;27:1693-8.
22. Sacks DG, Okano Y, Steen VD, et al. Isolated pulmonary hypertension in systemic sclerosis with diffuse cutaneous involvement: association with serum anti-U3RNP antibody. *J Rheumatol.* 1996;23:639-42.
23. Steen VD, Ziegler GL, Rodnan GP, et al. Clinical and laboratory associations of anticentromere antibody in patients with progressive systemic sclerosis. *Arthritis Rheum.* 1984;27:125-31.
24. Okano Y, Steen VD, Medsger TA Jr. Autoantibody to U3 nucleolar ribonucleoprotein (fibrillarin) in patients with systemic sclerosis. *Arthritis Rheum.* 1992;35:95-100.
25. Mitri GM, Lucas M, Fertig N, et al. A comparison between anti-Th/To- and anticentromere antibody-positive systemic sclerosis patients with limited cutaneous involvement. *Arthritis Rheum.* 2003;48:203-9.
26. Ulanet DB, Wigley FM, Gelber AC, et al. Autoantibodies against B23, a nucleolar phosphoprotein, occur in scleroderma and are associated with pulmonary hypertension. *Arthritis Rheum.* 2003;49:85-92.
27. Stupi AM, Steen VD, Owens GR, et al. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum.* 1986;29:515-24.
28. Steen VD, Graham G, Conte C, et al. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum.* 1992;35:765-70.
29. Dawson JK, Goodson NC, Graham DR, et al. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology (Oxford).* 2000;39:1320-5.
30. Aoki A, Kenmochi H, Hagiwara E, et al. Pulmonary hypertension in a patient with primary Sjogren's syndrome, Hashimotos's disease, and primary biliary cirrhosis [in Japanese]. *Nihon Rinsho Meneki Gakkai Kaishi.* 2000;23:462-9.
31. Raeside DA, Chalmers G, Clelland J, et al. Pulmonary artery pressure variation in patients with connective tissue disease: 24 hour ambulatory pulmonary artery monitoring. *Thorax.* 1998;53:857-62.
32. Falcoa CA, Alves IC, Chahade WH, et al. Echocardiographic abnormalities and antiphospholipid antibodies in patients with systemic lupus erythematosus. *Arq Bras Cardiol.* 2002;79:285-91.
33. Asherson RA, Higgenbottam TW, Dinh Xuan AT, et al. Pulmonary hypertension in a lupus clinic: experience with twenty-four patients. *J Rheumatol.* 1990;17:1292-8.
34. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection: comparison with primary pulmonary hypertension. *Circulation.* 1994;89:2722-7.
35. Hadengue A, Benhayoun MK, Lebrec D, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. *Gastroenterology.* 1991;100:520-8.
36. Pengo V, Lensing AWA, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;350:2257-64.
37. Viner SM, Bagg BR, Auger WR, et al. The management of pulmonary hypertension secondary to chronic thromboembolic disease. *Prog Cardiovasc Dis.* 1994;37:79-82.
38. D'Alonzo GE, Bower JS, Dantzker DR. Differentiation of patients with primary and thromboembolic pulmonary hypertension. *Chest.* 1984;85:457-61.
39. Fishman AJ, Moser KM, Fedullo PF. Perfusion lung scans vs pulmonary angiography in evaluation of suspected primary pulmonary hypertension. *Chest.* 1983;84:679-83.
40. Ryan KL, Fedullo PF, Davis GB, et al. Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. *Chest.* 1988;93:1180-5.
41. Steenhuis LH, Groen HJ, Koeter GH, et al. Diffusion capacity and haemodynamics in primary and chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2000;16:276-81.
42. Rafanan AL, Golish JA, Dinner DS, et al. Nocturnal hypoxemia is common in primary pulmonary hypertension. *Chest.* 2001;120:894-9.
43. Laffon E, Vallet C, Bernard V, et al. A computed method for noninvasive MRI assessment of pulmonary hypertension. *J Appl Physiol.* 2004;96:463-8.
44. Saba TS, Foster J, Cockburn M, et al. Ventricular mass index using magnetic resonance imaging accurately estimates pulmonary artery pressure. *Eur Respir J.* 2002;20:1519-24.
45. Bergin CJ, Hauschildt J, Rios G, et al. Accuracy of MR angiography compared with radionuclide scanning in identifying the cause of pulmonary arterial hypertension. *AJR Am J Roentgenol.* 1997;168:1549-55.
46. Hatabu H, Gefter WB, Axel L, et al. MR imaging with spatial modulation of magnetization in the evaluation of chronic central pulmonary thromboemboli. *Radiology.* 1994;190:791-6.
47. Boxt LM. MR imaging of pulmonary hypertension and right ventricular dysfunction. *Magn Reson Imaging Clin N Am.* 1996;4:307-25.
48. Frank H, Globits S, Glogar D, et al. Detection and quantification of pulmonary artery hypertension with MR imaging: results in 23 patients. *AJR Am J Roentgenol.* 1993;161:27-31.
49. Katz J, Whang J, Boxt LM, et al. Estimation of right ventricular mass in normal subjects and in patients with primary pulmonary hypertension by nuclear magnetic resonance imaging. *J Am Coll Cardiol.* 193;21:1475-81.
50. Waxman AB. Pulmonary function test abnormalities in pulmonary vascular disease and chronic heart failure. *Clin Chest Med.* 2001;751-8.
51. Janicki J, Weber K, Likoff M, et al. Exercise testing to evaluate patients with pulmonary vascular disease. *Am Rev Respir Dis.* 1984;129:S93-5.
52. Sun XG, Hansen JE, Oudiz RJ, et al. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation.* 2001;104:429-35.
53. Yasunobu Y, Oudiz RJ, Sun XG, et al. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest.* 2005;127:1637-46.
54. Hansen JE, Sun XG, Yasunobu Y, et al. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary hypertension. *Chest.* 2004;126:816-24.
55. 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.
56. Iwase T, Nagaya N, Ando M, et al. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in patients with chronic thromboembolic pulmonary hypertension. *Heart.* 2001;86:188-92.
57. Cahalin LP, Mathier MA, Semigran MJ, et al. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest.* 1996;110:325-32.
58. 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;161:487-92.
59. Wax D, Garofano R, Barst RJ: Effects of long-term infusion of prostacyclin on exercise performance in patients with primary pulmonary hypertension. *Chest.* 1999;914-20.