Surgical treatment of pulmonary hypertension: Lung transplantation

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ABSTRACT

Pulmonary hypertension (PH) is a serious and progressive disorder that results in right ventricular dysfunction that lead to subsequent right heart failure and death. When untreated the median survival for these patients is 2.8 years. Over the past decade advances in disease specific medical therapy considerably changed the natural history. This is reflected in a threefold decrease in the number of patients undergoing lung transplantation for PH which used to be main stay of treatment. Despite the successful development of medical therapy lung transplant still remains the gold standard for patients who fail medical therapy. Referral for lung transplant is recommended when patients have a less than 2-3 years of predicted survival or in NYHA class III or IV. Both single and bilateral lung transplants have been successfully performed for PH but outcome analyses and survival comparisons generally favor a bilateral lung transplant.

Key Words: pulmonary vascular disease, surgical procedure, lung transplant

INTRODUCTION

Pulmonary hypertension (PH), an abnormal elevation in pulmonary artery pressure, is defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise, with a pulmonary capillary wedge pressure ≤ 15 mmHg as measured by cardiac catheterization.[1] PH was traditionally divided into primary and secondary but this classification system has since been replaced by a system proposed by the World Health Organization in 1998 and most recently updated at Dana Point, California in 2008.[2] The current classification system categorizes PH into five major categories with further subdivisions in each category allowing patients to be placed in groups sharing similarities in clinical presentation, pathophysiology, and therapeutic approaches (Table 1). Regardless of its etiology, PH is a serious and progressive disorder that results in right ventricular dysfunction and impairment in activity tolerance that can lead to subsequent right-heart failure and death.

Pathobiology

PAH has a multifactorial pathophysiology.[3] Abnormalities in molecular pathways regulating the pulmonary vascular endothelial and smooth muscle cells have been described as underlying PAH with perturbations in vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. This includes inhibition of the voltage-regulated potassium channel,[4] mutations in the bone morphogenetic protein-2 receptor,[5] increased serotonin uptake in the smooth muscle cell,[6] increased angiopoietin expression in the smooth muscle cells,[7] and excessive thrombin deposition related to a procoagulant state.[8] As a result, there appears to be a loss of apoptosis of the smooth muscle cells allowing their proliferation, and the emergence of apoptosis-resistant endothelial cells that can obliterate the vascular lumen. Vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis contribute to increased pulmonary vascular resistance in PAH. Pulmonary vascular remodeling occurs at all levels of the vessel wall. Endothelial cells, smooth muscle cells, and fibroblasts as well as inflammatory cells and platelets may play a significant role in PAH.

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Table 1: Revised World Health Organization classification of pulmonary hypertension, Dana Point, California

Group 1: Pulmonary arterial hypertension
 Idiopathic (primary)
 Familial
  Related conditions: Collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins (e.g., Anorexigens, rapeseed oil, L-tryptophan, methamphetamine, and cocaine); other conditions: Thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
 Associated with significant venous or capillary involvement
  Pulmonary veno-occlusive disease
  Pulmonary-capillary hemangiomatosis
 Persistent pulmonary hyptertension of the newborn
Group 2: Pulmonary venous hypertension
 Left-sided atrial or ventricular heart disease
 Left-sided valvular heart disease
Group 3: Pulmonary hypertension associated with hypoxemia
 Chronic obstructive pulmonary disease
 Interstitial lung disease
 Sleep-disordered breathing
 Alveolar hypoventialtion disorders
 Chronic exposure to high altitude
 Developmental abnormalities
Group 4: Pulmonary hypertension due to chronic thrombotic disease or embolic disease
 Thromboembolic obstruction of proximal pulmonary arteries
 Thromboembolic obstruction of distal pulmonary arteries
 Pulmonary embolism (tumor, parasites, foreign material)
Group 5: Miscellaneous
 Sarcoidosis, pulmonary Langerhans'-cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Adapted from Simonneau et al.

Pulmonary vasoconstriction is believed to be an early component of the pulmonary hypertensive process and may be related to abnormal function of potassium channels and endothelial dysfunction.[4] Endothelial dysfunction leads to chronically impaired production of vasodilators such as nitric oxide and prostacyclin along with overexpression of vasoconstrictors such as endothelin.[9] Recent genetic and pathophysiologic studies have emphasized the relevance of several mediators in this condition, including prostacyclin,[10] nitric oxide,[11] endothelin,[12] angiopoietin,[7] serotonin,[13] and members of the transforming growth factor superfamily (TGF)-β.[5]

Pathophysiology

The pathophysiology of PH can be understood as a lethal cycle of increased pulmonary vascular resistance (as a result of any of the causes listed in the WHO classification scheme) leading to increased right ventricular performance and oxygen consumption with resultant right ventricular hypertrophy and dilatation, leading to decreased cardiac output and eventual right ventricular failure (Fig. 1).[14,15] In response to an increase in resistance within the pulmonary circulation, the right ventricle responds by increasing right ventricular systolic pressure as necessary to preserve cardiac output. Over time, the pulmonary vascular system responds with progressive remodeling that sustains and promotes PH.

Hypotension   Increased RVEDP

Reduced RV coronary blood flow

RV ischemia

Decreased cardiac output
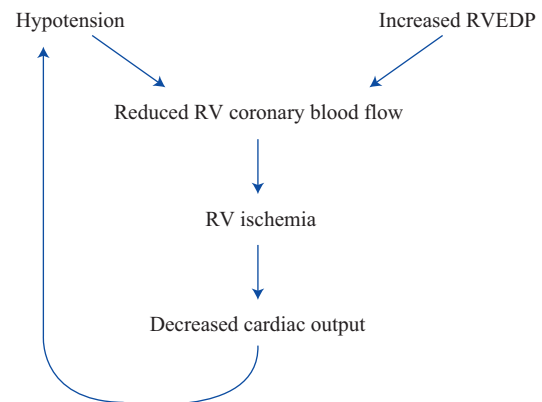
Figure 1: The downward spiral of pulmonary hypertension (adapted from Vigneswaran et al.).

The degree to which the right ventricle responds to such changes is dependent upon the age of the patient and rapidity of onset of PH. A large acute pulmonary embolism can result in right ventricular failure and shock whereas chronic thromboembolic disease of equal severity may result in only mild exercise intolerance.

The right ventricle is well designed to adapt to wide variations in preload owing to its anatomical structure and geometry, however these features are not suited to adequately deal with increases in afterload. One of the

key features to right ventricular adaptation to chronic pressure overload is hypertrophy due to increased wall stress (Laplace's Law).[15] Hypertrophy is greatest in the right ventricular outflow tract and worse in patients with decompensated function.[15] In the setting of increased afterload, right ventricular stroke volume decreases linearly with increasing resistance leading to eventual ventricular dilatation and consequent decreased right ventricular coronary blood flow at a time when oxygen consumption is increased.[16] Furthermore, right ventricular dilatation shifts the interventricular septum to the left, decreasing left ventricular preload and compliance and thus cardiac output. Recent data also suggests that hypoxemia may impair the ability of the right ventricle to make compensatory changes. These studies suggest that right ventricular failure occurs in PH when the myocardium becomes progressively ischemic due to excessive demands and inadequate right ventricular coronary blood flow.[16] The onset of peripheral edema and other clinical manifestations of right heart failure usually portend a poor outcome.[17]

Presenting signs and symptoms

Patients with PH may present with a myriad of cardiopulmonary symptoms however exertional dyspnea is the most frequent symptom and unexplained dyspnea should always raise suspicion. PH may be asymptomatic in the early stages and may be an incidental finding on echocardiogram. Chest pain and syncope are usually late symptoms. Patients may present signs and symptoms of right heart failure such as peripheral edema or ascites. A family history of PH, use of fenfluramine appetites suppressants, cocaine or amphetamines, prior history of deep vein thrombosis (DVT) or pulmonary embolism (PE), chronic liver disease or portal hypertension, HIV, thyroid disease, splenectomy, and sickle cell disease should be sought in all patients suspected to have PH. Physical exam findings include increased jugular venous pressure, a reduced carotid pulse, and a palpable right ventricular impulse. Most patients have an increased pulmonic component of the second heart sound, a right-sided fourth heart sound, and tricuspid regurgitation. Peripheral cyanosis and/or edema tend to occur in later stages of the disease.

Diagnosis and assessment of functional status

The goals of work-up in PH include confirmation of diagnosis, establishing an underlying cause, and quantifying severity with hemodynamics and functional impairment. All patients who appear to have PH after non-invasive testing should undergo right heart catheterization confirm the diagnosis, quantify the degree of hypertension (measurement of pulmonary artery pressure, cardiac output, and left ventricular filling pressure, underlying cardiac shunt) and undergo acute vasodilator testing.

Acute vasodilator testing, during catheterization defines the extent of pulmonary vasodilator reactivity and dictates prognosis and therapy. The majority of centers use inhaled nitric oxide (NO) as a pulmonary vasodilator (10-80 ppm).[18] A positive vasodilator response is defined as a decrease of at least 10 mmHg in mean PAP and achieving a mean PAP <40 mmHg, an increase or no change in cardiac output with no significant fall in blood pressure.[19] Patients who respond to acute vasodilator therapy can often be treated with calcium channel blockers and have a more favorable prognosis.[20] Echocardiography is helpful in confirming the diagnosis and excluding left-sided lesions as the cause of PH but is not specific enough to confirm a diagnosis of PH alone. Overall functional status assessed by symptoms (New York Heart Association [NYHA] functional class/World Health Organization functional class [WHO-FC]) and functional capacity assessed primarily by the six-minute walk test (6-MWT) – a very simple and reproducible submaximal exercise test that can be performed by a patient not tolerating maximal exercise tests. The 6-MWT has been the cornerstone functional test to evaluate treatment efficacy both in clinical trials and in daily clinical practice. In unselected patients (treated or not), a 6-MWT of less than 332 meters is associated with a worse prognosis in iPAH and has a strong independent association with mortality in patients with type 1 PH.[21,22]

Prognosis

The natural history of PH is dismal, with a reported median survival rate of 2.8 years when untreated.[23] Functional class remains a strong predictor of survival, with patients who are in NYHA functional class IV having a mean survival of less than six months. The cause of death is usually right ventricular failure, which is manifest by progressive hypoxemia, tachycardia, hypotension, and edema. Over the past decade, advances in medical therapy considerably changed the prognosis of the disease. Most expert centers discuss the notion of transplantation early after diagnosis and closely follow patients' symptoms, functional status – including the six minute walk test distance, and hemodynamics.[24] Benza et al. analyzed data from 2716 patients with PAH in the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) study to determine factors that may predict 1-year survival in patients with PAH awaiting transplantion. The authors found in a multivariable analysis that factors independently associated with increased mortality included pulmonary vascular resistance >32 Wood units, PAH associated with portal hypertension, a modified NYHA/WHO functional class IV, men >60 years of age, and family history of PAH.[25] Their data also confirmed an increased mortality risk in patients with renal insufficiency or any pericardial effusion on echocardiogram.[25]

Medical management of PH

Of all the conditions for which lung transplantation is performed, PH is the only one in which there have been significant strides made in medical management. This is seen by the ever-decreasing number of patients with PH who ultimately undergo transplantation. In 1990, approximately 10.5% of all lung transplants were for patients with PH whereas in 2001 only 3.6% of all lung transplants were performed in patients with this condition and most recently, 3.3% as reported by the ISHLT Transplant Registry in 2010.[26,27] Treatment of PH is individualized, based upon severity of functional impairment. As summarized in Table 2, there are currently eight FDA-approved therapies for WHO group 1 PAH.[28]

These medications include endothelin receptor antagonists (ERAs) (bosentatn and ambrisentan), phosphodiesterase-5 inhibitors (PDE5-I) (sildenafil and tadalafil), and prostanoid derivatives (epoprostenol, trepostinil, and iloprost). The latter group—the prostanoids introduced in the 1990s—have been the most important advance in the management of patients with PH. Chronic intravenous epoprostenol therapy leads to an improvement in exercise tolerance, hemodynamic measures, as well as survival in iPAH.[29,30] Initially intended to serve as a bridge to transplantation, with experience it has been realized that the need for transplantation can be averted in some cases. [31-34] Additionally, a select number of patients who have substantial reductions in pulmonary arterial pressure in response to short-acting vasodilators at the time of cardiac catheterization should be treated initially with calcium channel blockers.[20] Patients who respond favorably usually have dramatic reductions in pulmonary artery pressure and pulmonary vascular resistance associated with improved symptoms, regression of right ventricular hypertrophy and improved survival.[35] Anticoagulation with warfarin has been shown to provide a survival benefit in PH, even without documented thromboembolism. [36] Additionally, diuretic therapy relieves peripheral edema and may be useful in reducing right ventricular end diastolic pressure (RVEDP). Supplemental oxygen should be provided to alleviate dyspnea and right ventricular ischemia as hypoxemia is a potent pulmonary vasoconstrictor. A more comprehensive list of medical therapies is available in the most recent ACCP guidelines.[37]

Indications for lung transplantation

Despite the successful development of disease-specific medical therapies for PH which has reduced patient referral for lung transplant programs,[38] transplantation remains the gold-standard for patients who fail medical therapy. Survival among patients requiring treatment with intravenous prostacyclin is approximately 63% at 3 years[39,40] and up to 25% of patients with iPAH may fail

to improve on disease-specific therapy and the prognosis of patients who remain in WHO-FC III or IV is poor.[32,33] McLaughlin et al. describe a treatment algorithm based on a risk assessment based on various clinical variables (Table 3). Patients at highest risk should be considered for intravenous therapy as first-line therapy and immediate assessment for lung transplantation. Patients as lower risk are candidates for oral therapy and should be followed closely, and response to therapy reassessed in several months if treatment goals are not met.[41]

In general, referral for transplantation assessment is advisable when patients have a less than 50%, 2- to 3-year predicted survival or NYHA class III or IV level of function, or both.[24] With regards to PAH, most experts recommend transplantation early after diagnosis based on patients' symptoms, functional status—including the 6-MWT distance—hemodynamics.[24] The decision to list for transplant is made when functional status and hemodynamics decline to the point where survival without transplantation is likely to be compromised[24] (Table 4).

Type of transplantation

The appropriate surgical procedure for patients with

Table 2: US Food and Drug Administration-Approved medications for pulmonary hypertension

Name	Approved NYHA class
Bosentan (Tracleer)	NYHA II, III, IV
Ambrisentan (Letairis)	NYHA II, III, IV
Sildenafil (Revatio)	NYHA II, III, IV
Epoprostenol (Flolan)	NYHA III, IV
Treprostinil (Remodulin)	NYHA II, III, IV
Tadalafil (Adcirca)	NYHA I, II, III, IV
Iloprost (Ventavis)	NYHA III, IV
Treprostinil (Tyvaso)	NYHA III

NYHA: New York Heart Association

Table 3: Determinants of risk in patients with pulmonary hypertension

Lower	Determinants of risk	Higher
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (>400 m)	6 minute walk distance	Shorter (<300 m)
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion Significant RV dysfunction
Normal/near normal RAP and CI	Hemodynamics	High RAP, low CI

Adapted from McLaughlin et al.

Table 4: ISHLT guidelines for lung transplantation

Persistent NYHA class III or IV on maximal medical therapy
Low (<350 meter) or declining 6-MWT
Failing therapy with intravenous epoprostenol, or equivalent
Cardiac index of less than 2 liters/min/m^2
Right atrial pressure exceeding 15 mmHg

NYHA: New York Heart Association; **ISHLT:** International Society for Heart and Lung Transplantation

iPAH and secondary PAH has been a topic of longstanding debate. Single lung transplant (SLT), bilateral lung transplant (BLT), and heart-lung transplant (HLT) are all used in the treatment of PH. HLT was originally the standard procedure for patients with PH until the 1990's and is still the preferred treatment for PH patients with irreversible heart disease. However the number of adult HLT have declined significantly in recent years[42-50] to about 70 to 90 per year. It has largely been replaced by bilateral lung transplant, now the most commonly used form of transplantation PH patients. This change was multifactorial: results with SLT or BLT for PH are comparable to or better than HLT, right heart dysfunction improves following SLT or BLT due to right ventricular recovery with the rapid reduction in pulmonary vascular resistance after lung transplantation, as well as ethical and pragmatic concerns centered on donor shortages and organ distribution.[51]

In 2008, according to the Official Lung and Heart-Lung Transplant Report of the Registry of the International Society for Heart and Lung Transplantation reported 73 heart-lung transplants and 2,769 lung transplant procedures. Among these, approximately one-quarter of heart-lung transplants were performed with PH as the primary diagnosis and while less than 5% of isolated lung transplant procedures were performed for PH.[52] Among patients undergoing isolated lung transplantation, BLT is used much more frequently–accounting for 91% of transplants performed for PH and the remaining 9% consisting of SLT.[52]

Outcomes following isolated lung transplantation for pulmonary hypertension

For all lung transplant recipients, overall unadjusted survival rates were 79% at one year, 63% at three years, 52% at five years, and 29% at 10 years.[52] Survival rates at three months after lung transplantation were lowest for iPAH (76%) as well as idiopathic pulmonary fibrosis (85%) and highest for cystic fibrosis (90%) and chronic obstructive pulmonary disease (91%).[52] In contrast, among patients surviving at least one year, diagnoses of iPAH, cystic fibrosis, sarcoidosis, and emphysema had significantly better survival at five and 10 years following lung transplantation than those with chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis.

The evidence regarding the optimal transplant procedure for PH is remains weak. Available data is largely composed of single center studies. Both SLT and BLT have been performed successfully for PH however outcome analyses and survival comparisons generally favor BLT. There is a trend towards a survival benefit with BLT in the ISHLT registry, however it does not reach statistical significance.

Those who support SLT argue that SLT is easier to perform technically, has less morbidity and mortality versus BLT and HLT, less ischemic time and bypass time with resultant better early graft function, has improved early survival, and will allow more patients to receive lung transplants. Hemodynamics following SLT for PH are characterized by a rapid and sustained drop in pulmonary artery pressures, substantial improvement in right ventricular function, and a preponderance (>90%) of pulmonary blood flow to the allograft as a result of high pulmonary vascular resistance in the remaining native lung.[53-55] This leads to a postoperative situation in which ventilation is evenly divided between the allograft and native lung while perfusion is almost entirely directed to the allograft. Any complication in the allograft (e.g., pneumonia, primary graft dysfunction, rejection) can result in severe ventilation-perfusion mismatch and hypoxemia.

Most centers favor BLT because of the physiologically increased functional reserve, making patients less prone to respiratory insufficiency with subsequent insult.[47,56] Proponents of BLT have argued that bilateral lung transplants result in less ventilation perfusion (V/Q) mismatches, are easier to care for in the perioperative period, will enable more "marginal lungs" to be utilized, will provide better overall lung function, are protective against the physiologic manifestations of bronchiolitis obliterans, and have a better long-term survival. In its most recent publication, the ISHLT registry reported a significantly better survival in the bilateral lung transplantation group as compared with the single lung transplant in patients with iPAH.[52] The Pittsburgh group compared recipients of SLT versus BLT with PH and found similar functional status and postoperative recovery (hemodynamics, duration of mechanical ventilation, intensive care unit/hospital length of stay, and incidence of acute/chronic rejection).[43] They did, however, report that SLT recipients had a significantly lower PaO$_2$/FiO$_2$ at one hour and higher mean pulmonary artery pressure at 12 and 24 hours.[43] Bando et al. concluded that despite significantly shorter cardiopulmonary bypass duration in their cohort, SLT recipients with underlying PH had significantly less functional recovery (less reduction in mean pulmonary artery pressure and increase in cardiac index) and higher graft mortality compared with BLT and HLT recipients.[45] The Hopkins experience evaluated 15 patients with iPAH and found BLT to have a highly

significant survival advantage compared with SLT at 4 years of follow-up.[51] The most recent ISHLT registry reported 788 iPAH lung transplant recipients of which 91% were BLT, highlighting the continuing trend at most centers favoring BLT versus SLT for iPAH.[27]

Outcomes following heart-lung transplantation for pulmonary hypertension

According to the 2009 ISHLT registry report comparing the outcome of HLT with BLT for pulmonary hypertension demonstrated similar survival between the two groups. Of 2712 adult patients who underwent heart-lung transplantation between 1982 and 2007 survival rates of 72 percent at three months and 64 percent at one year. Survival for HLT was less than with lung transplantation alone (89% and 79%, respectively, in the era from 1994 to 2007). However, overall survival five years and ten years was 43% and 28%, which was comparable to isolated lung transplantation. Among HLT patients who survived one year, there was a low but steady mortality rate with a survival conditional half-life (contingent on survival to one year) of 9.2 years.[57]

CONCLUSIONS

Lung transplant is an effective form of treatment for patients with PH who have exhausted all medical therapy. BLT is the current choice of transplantation in this patient population.

REFERENCES

1. Archer SL, Michelakis ED. Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension. N Engl J Med 2009;361:1864-71.
2. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54 (1 Suppl):S43-54.
3. Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest 2008;118:2372-9.
4. Yuan JX, Aldinger AM, Juhaszova M, Wang J, Conte JV Jr, Gaine SP, et al. Dysfunctional voltage-gated K+ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. Circulation 1998;98:1400-6.
5. Newman JH, Wheeler L, Lane KB, Loyd E, Gaddipati R, Phillips JA 3rd, et al. Mutation in the gene for bone morphogenetic protein receptor II as a cause of primary pulmonary hypertension in a large kindred. N Engl J Med 2001;345:319-24.
6. Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. J Clin Invest 2001;108:1141-50.
7. Du L, Sullivan CC, Chu D, Cho AJ, Kido M, Wolf PL, et al. Signaling molecules in nonfamilial pulmonary hypertension. New Engl J Med 2003;348:500-9.
8. Eisenberg PR, Lucore C, Kaufman L, Sobel BE, Jaffe AS, Rich S, et al. Elevations in fibrinopeptide A indicative of pulmonary vascular thrombosis in patients with primary pulmonary hypertension. Circulation 1990;82:841-7.
9. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328:1732-9.
10. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999;159:1925-32.
11. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995;333:214-21.
12. Cacoub P, Dorent R, Nataf P, Carayon A, Riquet M, Noe E, et al. Endothelin-1 in the lungs of patients with pulmonary hypertension. Cardiovasc Res 1997;33:196-200.
13. Egermayer P, Town GI, Peacock AJ. Role of serotonin in the pathogenesis of acute and chronic pulmonary hypertension. Thorax 1999;54:161-8.
14. Rich S. Pulmonary arterial hypertension. In: Vigneswaran WT, editor. Lung Transplantation. Colchester, UK: Informa Healthcare, 2010. p. 65-74.
15. Simon MA, Pinsky MR. Right ventricular dysfunction and failure in chronic pressure overload. Cardiol Res Pract 2011;2011:568095.
16. Vlahakes G, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlation. Circulation 1981;63:87-95.
17. 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;115:343-9.
18. Archer SL, Michelakis ED. An evidence-based approach to the management of pulmonary arterial hypertension. Curr Opin Cardiol 2006;21:385-92.
19. Badesch DB, Abman SH, Ahearn GS, Barst RJ, McCrory DC, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126(1 suppl):35S-62S.
20. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76-81.
21. Wensel R, Opitz CF, Anker SD, Winkler J, Höffken G, Kleber FX, et al. Assessment of survival in patients with primary pulmonary hypertension: Importance of cardiopulmonary exercise testing. Circulation 2002;106:319-24.
22. 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;161:487-92.
23. Raymond RJ, Hinderliter AL, Willis PW, Ralph D, Caldwell EJ, Williams W, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. J Am Coll Cardiol 2002;39:1214-9.
24. Galie N, Hoeper MM, Humbert M. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009;30:2493-537.
25. Benza RL, Gomberg-Maitland M, Miller DP, Frost A, Frantz RP, Foreman AJ, et al. The REVEAL risk score calculator in newly diagnosed patients with pulmonary arterial hypertension. Chest 2011 [In press].
26. The International Society for Heart and Lung Transplantation. Heart/Lung Transplant Registry. Available from: http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry [Last accessed on 2005 Feb 24].
27. Christie JD, Edwards LB, Kucheryavaya AY, Aurora P, Dobbels F, Kirk R, et al. The registry of the International Society for Heart and Lung Transplantation: Twenty-seventh official adult lung and heart-lung transplant report—2010. J Heart Lung Transplant 2010;29:1104-18.
28. Saggar R, Lynch JP, Belperio JA, Weigt SS, Derhovanessian A, Gupta S, et al. Pulmonary arterial hypertension and lung transplantation. Semin Respir Crit Care Med 2010;31:147-60.
29. Magnani B, Galie N. Prostacyclin in primary pulmonary hypertension. Eur Heart J 1996;17:18-24.
30. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. The Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296-302.
31. Kuhn KP, Byrne DW, Arbogast PG, Doyle TP, Loyd JE, Robbins IM. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med 2003;167:580-6.
32. 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;40:780-8.
33. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation 2002;106:1477-82.
34. Conte JV, Gaine SP, Orens JB, Harris T, Rubin LJ. The influence of continuous intravenous prostacyclin therapy for primary pulmonary

hypertension on the timing and outcome of transplantation. J Heart Lung Transplant 1998;17:679-85.

35. Sitbon O, Humbert M, Jais X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.

36. Frank H, Mlczoch J, Huber K, Schuster E, Gurtner HP, Kneussl M, et al. The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest 1997;112:714-21.

37. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based clinical practice guidelines. Chest 2007;131:1917-28.

38. Keogh AM, Mayer E, Benza RL, Corris P, Dartevelle PG, Frost AE, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. J Am Coll Cardiol 2009;54(1 Suppl):S67-77.

39. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation 2006;114:1417-31.

40. Department of Health. Hospital Episode Statistics. Available from: htttp://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937. [Last accessed on 2007 Jul 15].

41. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the Amercian College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association devleoiped in collaboration with the American College of Chest Physicians; Amercian Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573-619.

42. Pasque MK, Trulock EP, Cooper JD, Triantafillou AN, Huddleston CB, Rosenbloom M, et al. Single lung transplantation for pulmonary hypertension: single institution experience in 34 patients. Circulation 1995;92:2252-8.

43. Gammie JS, Keenan RJ, Pham SM, McGrath MF, Hattler BG, Khoshbin E, et al. Single versus double lung transplantation for pulmonary hypertension. J Thorac Cardiovasc Surg 1998;115:397-403.

44. Bando K, Keenan RJ, Paradis IL, Konishi H, Komatsu K, Hardesty RL, et al. Impact of pulmonary hypertension on outcome after single lung transplantation. Ann Thorac Surg 1994;58:1336-42.

45. Bando K, Armitage JM, Paradis IL, Keenan RJ, Hardesty RL, Konishi H, et al. Indications for and results of single, bilateral, and heart-lung transplantation for pulmonary hypertension. J Thorac Cardiovasc Surg 1994;108:1056-65.

46. Chapelier A, Vouhe P, Macchiarini P, Lenot B, Cerrina J, Le Roy Ladurie F, et al. Comparative outcome of heart-lung and lung transplantation for pulmonary hypertension. J Thorac Cardiovasc Surg 1993;106:229-307.

47. Birsan T, Zuckermann Z, Artermiou O, Senbaklavci O, Taghavi S,

Wieselthaler G, et al. Bilateral lung transplantation for pulmonary hypertension. Transplant Proc 1997;29:2892-4.

48. Whyte RI, Robbins RC, Altinger J, Barlow CW, Doyle R, Theodore J, et al. Heart-lung transplantation for primary pulmonary hypertension. Ann Thorac Surg 1999;67:937-42.

49. Mikhail G, Al-Kattan K, Banner N, Mitchell A, Radley-Smith R, Khaghani A, et al. Long-term results of heart lung transplantation for pulmonary hypertension. Transplant Proc 1997;29:633.

50. Ueno T, Smith JA, Snell GI, Williams TJ, Kotsimbos TC, Rabinov M, et al. Bilateral sequential single lung transplantation for pulmonary hypertension and Eisenmenger's syndrome. Ann Thorac Surg 2000;69:381-7.

51. Conte JV, Borja MJ, Patel CB, Yang SC, Jhaveri RM, Orens JB. Lung transplantation for primary and secondary pulmonary hypertension. Ann Thorac Surg 2001;72:1673-80.

52. Taylor DO, Edwards LB, Aurora P, Christie JD, Dobbels F, Kirk R, et al. The registry of the International Society for Heart and Lung Transplantation: Twenty-fifth official adult lung and heart-lung transplant report—2008. J Heart Lung Transplant 2010;27:943-56.

53. Griffith BP, Hardesty RL, Armitage JM, Hattler BG, Pham SM, Keenan RJ, et al. A decade of lung transplantation. Ann Surg 1993;218:310-20.

54. Katz W, Gasior TA, Quinlan JJ, Lazar JM, Firestone L, Griffith BP, et al. Immediate effects of lung transplantation on right ventricular morphology and function in patients with variable degrees of pulmonary hypertension. J Am Coll Cardiol 1996;27:384-91.

55. Pasque MK, Trulock EP, Kaiser LR, Cooper JD. Single-lung transplantation for pulmonary hypertension. Three-month hemodynamic follow-up. Circulation 1991;84:2275-9.

56. Levine SM, Jenkinson SG, Bryan CL, Anzueto A, Zamora CA, Gibbons WJ, et al. Ventilation-perfusion inequalities during graft rejection in patients undergoing single lung transplantation for primary pulmonary hypertension. Chest 1992;101:401-5.

57. Afshar K, Weill D, Valentine V, Dhillon G. Comparison of double-lung and heart-lung transplantation for pulmonary hypertension: Analysis of the UNOS database. J Heart Lung Transplant 2009;28:S310.