A Study of Etio-Clinical and Echocardiographic Profile of Patients Presenting with Pulmonary Hypertension

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ABSTRACT

INTRODUCTION: Pulmonary hypertension encompasses a heterogenous group of diseases with common clinical manifestation characterized by a progressive increase in pulmonary vascular load, leading to marked increase in pulmonary artery pressure, right ventricular failure and premature death. It is essential for medical practitioners to have a high index of clinical suspicion of this devastating disease as early diagnosis may affect the survival.

AIMS AND OBJECTIVES: To study the etiology, clinical presentation, comorbid conditions and echocardiographic findings of patient with pulmonary hypertension.

MATERIALS AND METHODS: About 133 patients who got admitted in wards or followed in OPD of the Department of Medicine/Centre of Cardiology and Department of Tuberculosis and Respiratory Diseases, Jawaharlal Nehru Medical College Hospital, AMU, Aligarh were studied between July 2011 and July 2013. A detailed history and complete physical examination were carried out. Echocardiography was done to look for the presence of pulmonary hypertension and to look for any obvious cause on echo.. Patients were evaluated for the etiology of pulmonary hypertension with complete blood count (CBC), Renal function test (RFT), Liver function test (LFT), Thyroid function test (TFT), HIV ELISA, Anti nuclear antibodies ANA, Chest X Ray, USG abdomen, High resolution Computed Tomography of the Chest (HRCT) and Pulmonary function testing (PFT). Clinical grading of pulmonary hypertension severity was done according to the WHO functional classification. All patients underwent a complete transthoracic echocardiographic study including two-dimensional, M-Mode, color flow and spectral Doppler echocardiography.

RESULTS: Of the total 133 patients, 69 (51.9%) were males and 64 (48.1%) were females. Mean age of patients was 43.47±17.44 years. 21.8% patients were in NYHA class II, 45.9% were in NYHA class III and 32.3% were in NYHA class IV. Mean ages of patients in NYHA class II, III and IV were 42.14±18.49, 45.39±16.55 and 41.63±18.09 years respectively, with a p value of <0.001. The mean PASP in NYHA class II, III and IV were 45.21±9.46 mmHg, 66.25±11.49 mmHg and 91.35±15.94 mmHg respectively, with a p-value of <0.001. The mean pulmonary gradient in these groups were: 34.0±13.28mmHg, 44.62±13.52 mmHg and 64.18±17.7 mmHg respectively, with a p-value of 0.029. Amongst the etiological factors studied, 4 males and 5 females had congenital heart disease, 16 males and 23 females had valvular heart disease, 36 males and 22 females had COPD, 1 male and 5 females had primary pulmonary hypertension, 10 males and 6 females had cardiomyopathy.

CONCLUSION: 133 patients presenting with pulmonary hypertension were studied for demographic, clinical, etiological and echocardiographic data. Males outnumbered females, the association between age and NYHA class was found to be statistically significant. The most common etiology was COPD, followed by Valvular heart disease. Sildenafil was found to improve symptoms and exercise capacity.

INTRODUCTION

Pulmonary hypertension encompasses a heterogenous group of diseases with common clinical manifestations characterized by a progressive increase in pulmonary vascular load, leading to marked increase in pulmonary artery pressure, right ventricular failure and premature death. Pulmonary hypertension is a routinely made diagnosis in cardiology and pulmonary clinics. It is essential for medical practioners to have a high index of clinical suspicion of this devastating disease as early diagnosis may affect the survival. Pulmonary hypertension is defined as mean pulmonary artery pressure more than 25 mm

Hg [1]. World health organization has endorsed the clinical classification based on pathologic, pathophysiologic and therapeutic characteristics [2]. The total pulmonary hypertension burden of the disease is substantial as it represents an end stage of multiple disease processes such as left sided heart disease, chronic lung disease, as well as primary pulmonary hypertension which is very rare [3]. Most of the patients who are diagnosed with pulmonary hypertension on routine testing i.e. echocardiography end up having left heart disease (nearly 80%), some with lung disease and hypoxia (10%), and only a small minority (4%) have primary pulmonary hypertension.

Data from registries estimate the prevalence at around 15-50 cases/million adults and its incidence at around 2.4 cases/million adults/year [4]. Idiopathic pulmonary artery hypertension (IPAH) and familial pulmonary artery hypertension (previously known as primary pulmonary hypertension) are rare diseases with prevalence of around 6 cases/million. Familial cases account for 5-10% of all pulmonary artery hypertension. Pulmonary hypertension has been associated with environmental factors such as the use of drugs and toxins. Anorexigens (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) have been associated with pulmonary hypertension [5].

Selected patient populations are at increased risk of developing pulmonary hypertension:

1-Patients with connective tissue disease, especially limited cutaneous form of systemic sclerosis. The prevalence of pulmonary hypertension in systemic sclerosis is around 10-15% [6].Other causes are systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, dermatomyositis etc.

2- Human immunodeficiency virus (HIV) infection is associated with around 0.5% cases of pulmonary hypertension [7].

3-Patients of cirrhosis and portal hypertension are at increased risk of developing pulmonary hypertension. Incidence is around 5% of patients referred for liver transplantation [8].

4- Congenital heart disease may lead to pulmonary hypertension when the underlying systemic to pulmonary shunt is not corrected. Most commonly it occurs with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures e.g. ventricular septal defect and patent ductus arteriosus. However, high blood flow alone, as in atrial septal defect may lead to pulmonary hypertension [9].

The essential noninvasive test in the screening and evaluation of pulmonary hypertension is Doppler echocardiography. Echocardiography can help not only to estimate right ventricular function, but also exclude the presence of left-heart disease. Doppler assessments can be used to estimate the right ventricular systolic pressure and to evaluate for the presence of intracardiac shunts and other forms of congenital heart disease [10]. The initial evaluation of patients with pulmonary hypertension should consist of testing to confirm the diagnosis, a search for causative disorders and complications from the disease, and a determination of the severity of the disease.

Left-heart disease, valvular heart disease, and parenchymal lung disease deserve special attention during this initial period of evaluation as they are common causes of pulmonary arterial pressure elevation and right ventricular failure. A detailed history should be taken from the patient in an attempt to define the severity, duration, and degree of acceleration in symptom severity. The patient should also be questioned about drugs of abuse, herbal medicines and supplements, and prescription drugs including appetite suppressants and anorexigens.

EVALUATION OF A PATIENT WITH SUSPECTED PULMONARY HYPERTENSION

Essential Evaluation	Contingent Evaluation
History and physical examination	Transesophageal echo (TEE)
Chest x-ray (CXR)	Echo with bubble study
Electrocardiogram (ECG)	CT chest ± high resolution
Pulmonary function testing(PFT)	Pulmonary angiogram
Ventilation-perfusion scan (V/Q)	Arterial blood gas
Transthoracic echo (TTE)	Cardiac MRI
Blood tests: HIV, TFTs, LFTs, ANA	Blood tests: Uric acid, BNP
Six-minute walk test (6MWD)	Polysomnography
Overnight oximetry	Cardiopulmonary exercise
Right heart catheterization (RHC)	Open lung biopsy

MATERIALS AND METHODS

133 patients who got admitted in wards or followed in OPD of the department of Medicine/Centre of Cardiology and Department of Tuberculosis and Respiratory Diseases, Jawaharlal Nehru Medical College Hospital, AMU, Aligarh were studied between July 2011 and July 2013. A detailed history and complete physical examination were carried out. Echocardiography was done to look for the presence of pulmonary hypertension and to look for any obvious cause on echo. Patients were then evaluated for the etiology of pulmonary hypertension with complete blood count (CBC), Renal function test (RFT), Liver function test (LFT), Thyroid function test (TFT), HIV ELISA, Anti nuclear antibodies (ANA), Chest X Ray, USG abdomen, High Resolution Computed Tomography of the Chest (HRCT) and Pulmonary function test (PFT). Clinical grading of pulmonary hypertension severity was done according to the WHO functional classification.

All patients underwent a complete transthoracic echocardiographic study including two-dimensional, M-Mode, color flow and spectral Doppler echocardiography. Standard two-dimensional echocardiographic evaluation of right atrium (RA) and right ventricle (RV) size and function was performed. The right atrium and right ventricle were visualized by the apical four chamber view. RA size was evaluated using linear dimensions in the minor axis. Modified Simpson's rule was employed for estimating RV area. In addition, right ventricular end-diastolic (RV EDA) and end-systolic areas (RV ESA) were measured from the apical 4-chamber view to calculate right ventricular fractional area change (RV FAC). The main pulmonary artery (MPA) and ascending aorta were optimally visualized using the parasternal long axis views. The pulmonary artery size was measured below the pulmonic valve. M-mode and two dimensional echocardiography were used to document presence or absence of pericardial effusion. The free fluid in the pericardial cavity was visualized as an echo-free space using the parasternal long axis and short axis views. Isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ejection time (ET) were measured across the tricuspid valve using the pulsed wave Doppler echocardiography during the tricuspid valve flow.

Paradoxical septal motion was visualized in the parasternal long axis view and the 'D' sign was visualized by the parasternal short axis view as a flattening of the septum. Pulmonary artery systolic pressures (PASP) were estimated using the approach of calculating the systolic pressure gradient between right ventricle and right atrium by the maximum velocity of the tricuspid regurgitant jet in continuous wave. Doppler study was done using the modified Bernoulli equation and then adding to this value an estimated right atrial pressure based on both, the size of the inferior vena cava and the change in caliber of this vessel with respiration. M mode echocardiography was used to study the 'a' wave of the pulmonary valve and midsystolic notching or closure of the valve. Contrast study with agitated normal saline was done to rule out congenital or acquired shunt lesions.

Statistical Analysis

All statistical data were analysed using SPSS version 20. Chi square test was used for comparison of categorical variables, while continuous variables were compared using the student t test for independent groups. ANOVA with Scheffe's post hoc analysis was used for comparison of means between 3 or more groups. All p- values were two-tailed and and p values < 0.05 were considered statistically significant. All confidence levels were calculated at 95% level.

RESULTS

The mean age of patients was 43.47±17.44 years. Maximum number of patients (39.1%) was in the 50 to 70 year age group. Table 1 shows age-wise distribution of patients in the study group. Out of the total 133 patients of pulmonary hypertension studied, 69 (51.9%) were males and 64 (48.1%) were females (Table 2). 29 (21.8%) patients were found to be in NYHA class II, 61 (45.0%) were found to be in NYHA class III and 43 (31.3%) were found to be in NYHA class IV. No patients presented with NYHA class I (Table 3). Mean ages of patients in NYHA class II, III and IV were 42.14±18.49, 45.39±16.55 and 41.63±18.09 years respectively. The association between NYHA class and age was found to be statistically significant with a p-value of <0.001 (Table 4).

Table 1: Age-wise distribution of cases

AGE IN YEARS	CASES	
	NO.	%
LESS THAN 20 YEARS	13	9.8

20-29Y	20	15
30-49Y	43	32.3
50-70Y	52	39.1
MORE THAN 70 YEARS	5	3.8
TOTAL	133	100
MEAN	43.47	
S.D.	17.44	

Table 2. Sex Distribution

SEX	CASES	
	NO.	%
MALE	69	51.9
FEMALE	64	48.1
TOTAL	133	100

Table 3. Distribution of patients according to NYHA functional class

NYHA FUNCTIONAL CLASS	CASES	
	NO	%
I	-	-
II	29	21.8
III	61	45.9
IV	43	32.3
Total	133	100

Table 4. Association between NYHA class and age

NYHA FUNCTIONAL CLASS	AGE IN YEARS	
	MEAN	S.D
II	42.14	18.49
III	45.39	16.55
IV	41.63	18.09
'p'	<0.001	

Out of the 29 patients in NYHA class II, 12 (41.14%) were males and 17 (58.6%) were females. In NYHA class III, 33 (%$.1%) were males and 28 (45.9%) were females. Similarly, in NYHA class IV, out of the total 43 patients, 24 (55.8%) were males and 19 (44.2%) were females (Table 5).

Table 5. Sex distribution among NYHA classes

NYHA FUNCTIONAL CLASS	MALE		FEMALE	
	NO.	%	NO.	%
II	12	41.4	17	58.6
III	33	54.1	28	45.9
IV	24	55.8	19	44.2

Statistically significant correlations were found between NYHA functional class and pulmonary gradient (PG) and pulmonary artery pressure (PSAP) on echocardiography (Table 6). The mean PASP in NYHA class II, III and IV were 45.21±9.46 mmHg, 66.25±11.49 mmHg and 91.35±15.94 mmHg respectively, with a p-value of <0.001. The mean pulmonary gradient in these groups were: 34.0±13.28mmHg, 44.62±13.52 mmHg and 64.18±17.7 mmHg respectively, with a p-value of 0.029. All the 133 patients (100%) had dyspnea on exertion and cough with sputum. So, these were the most common symptoms of presentation. The next most common symptoms were palpitations and pedal edema, each found in 121 patients (91%). The distribution of patients according to symptoms is shown in table 7. The most common etiology of pulmonary hypertension was found to be chronic obstructive pulmonary disease (COPD). It was found in 36 (52.2%) of males and 22 (34.4%) of females presenting with pulmonary hypertension.

Table 6. Relationship between NYHA Functional Classification and echocardiographic indices

Parameter	NYHA Classification						'p'
	II		III		IV		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
PG mm/Hg	34.0	13.28	44.62	13.53	64.18	17.7	0.029
PASP mm/Hg	45.21	9.46	66.25	11.49	91.35	15.94	<0.001

Amongst the other etiological factors studied, 4 males and 5 females had congenital heart disease, 16 males and 23 females had valvular heart disease, 1 male and 5 females had primary pulmonary hypertension, 10 males and 6 females had cardiomyopathy. Table 8 shows the distribution of patients according to etiological factors. The echocardiographic indices were studied in detail among patients with different etiologies. The mean PSAP was highest among patients with primary pulmonary hypertension (82.1±17.97 mmHg), followed by pulmonary embolism (80.0±14.14 mmHg). The PSAP was lowest among patients with cardiomyopathies (56.6±14.32 mmHg). The pulmonary gradient was highest among patients with pulmonary embolism (58.0±12.7 mmHg), followed by primary pulmonary hypertension (54.6±18.04 mmHg). These associations were found to be statistically significant except for thromboembolic disease (p-vale+ 0.079). Table 9 shows the association between echocardiographic factors (PSAP & PG) and different etiologies of pulmonary hypertension.

Table 7.   Distribution of patients according to symptoms

Symptoms	CASES	
	NO.	%
Dyspnea on exertion	133	100
Chest Pain	55	41.4
Cough / Sputum	133	100
Palpitations	121	91
Pedal edema	121	91
Anasarca	21	15.8
Hemoptysis	20	15

Around 25 patients were put on oral sildenafil. These patients were then followed up for relief of symptoms. All the 25 patients reported back with improved symptoms. These patients also performed better on 6 minute walk test, compared to baseline at presentation. The echocardiographic indices (PSAP and PG) also showed improvement in all patients put on oral sildenafil.

Table 8. Distribution of patients according to etiology of pulmonary hypertension

ETIOLOGY		CASES			
		MALE		FEMALE	
		NO.	%	NO.	%
CONGENITAL HEART DISEASES	ASD	2	2.9	5	7.8
	VSD	1	1.4	-	-
	TAPVC	1	1.4	-	-
VALVULAR HEART DISEASES	RHD/MS	14	20.3	19	29.7
	RHD/MR	2	2.9	4	6.3
	RHD/AS	-	-	1	1.6
CHRONIC OBSTRUCTIVE LUNG DISEASES		36	52.2	22	34.4
PRIMARY PULMONARY HYPERTENSION		1	1.4	5	7.8
THROMBOEMBOLIC DISEASES		1	1.4	1	1.6
CARDIOMAYOPATHY	DCMP	9	13.0	6	9.4
	RCMP	1	1.4	-	-
CHRONIC KIDNEY DISEASE		1	1.4	-	-
MISCELLANEOUS		-	-	1	1.6

Table 9. Association between echocardiographic factors and different etiologies of pulmonary hypertension

ETIOLOGY	ECHOCARDIOGRAPHIC PARAMETERS					
	PSAP mm/Hg			PG mm/Hg		
	MEAN	SD	p- value	MEAN	SD	p- value
CONGENITAL HEART DISEASES	61.89	24.62	<0.001	46.34	23.33	<0.001
VALVULAR HEART DISEASES	68.87	19.91	<0.001	40.45	18.45	<0.001
CHRONIC OBSTRUCTIVE LUNG DISEASES	74.13	22.07	<0.001	53.08	19.16	<0.001
CARDIOMAYOPATHY	56.6	14.32	<0.001	39.5	12.97	<0.001
THROMBOEMBOLIC DISEASES	80.0	14.14	0.068	58.0	12.7	0.079
PRIMARY PULMONARY HYPERTENSION	82.1	17.97	0.012	54.6	18.04	0.001

DISCUSSION

Mean age of patients in the current study was 43.47±17.44 years. Earlier studies have reported higher mean age of patients presenting with pulmonary hypertension. In a previous study, Shapiro et al have reported a mean age of 49±18 years [11]. In yet another study by David et al, mean age was reported to be 53±14 years [12]. Raymond et al have also reported a mean age of 50.4±16.8 years [13]. Thus the mean age was relatively less in the current study, compared to earlier studies. This could be explained by the fact that, the previous studies cited above have been conducted on Western populations, where the incidence of valvular heart disease and chronic obstructive pulmonary disease is lesser compared to our study population, and therefore our patients were relatively younger at presentation compared to those studies. Rich et al have however reported a younger age of presentation (36±15 years). This is in contrast to our study, as well as most other earlier studies [14].

In a previous study, mean age of men was reported to be 49 years and that of women was reported to be 51 years [11]. In the current study, the mean age of men with pulmonary hypertension was 43.46±17.44 years, while that of women was 39.75±17.97 years. Thus the age of women was much lesser compared to previous studies. This could also be explained by higher incidence and earlier presentation of valvular heart disease in our population. In the current study, the highest number of patients has been reported in the 50-70 year age group (39.1%). This is in contrast to a previous study by David et al [12]. They have reported the highest number of patients (83.1%) in the 19-64 year age group. This difference may be attributed to the fact that the incidence of valvular heart disease is much lesser in those populations and congenital heart diseases (which present at earlier ages) are more common in those populations. They have reported only 12.8% patients in the age group of 65-74 years.

In the current study, males outnumbered the females (51.9% males vs. 48.1% females). This is in contrast to most previous studies, which have reported a higher incidence of pulmonary hypertension in females. Shapiro et al have reported 78% females [11]. Charles D et al have also reported 78% females [15]. David et al and Raymond et al have reported 79.5% and 78.6% females respectively in their studies [12, 13].

The male:female ratio in the current study was 1.07:1. This was higher than most previous studies, but closer to that reported by Rich et al i.e. 1.7:1 [14]. In the present study, 29 (21.8%) patients were found to be in NYHA class II, 61 (45.0%) were found to be in NYHA class III and 43 (31.3%) were found to be in NYHA class IV. No patients presented with NYHA class I. Thus, the maximum number of patients was seen in the NYHA class III. This is in concert with many previous studies. Charles D et al have shown 59% patients in NYHA class III; David et al have reported this figure to be 50% and Raymond et al have reported it to be 48.2% [12, 13]. Although we have seen a maximum number of patients with

NYHA class III, the overall number of females was maximum in NYHA class II. In the present study, mean ages of patients in NYHA class II, III and IV were 42.14±18.49, 45.39±16.55 and 41.63±18.09 years respectively. The association between NYHA class and age was found to be statistically significant with a p-value of <0.001. This was also comparable to previous studies [15].

The most common symptom at presentation was dyspnea on exertion in the present study (seen in 100% patients); followed by cough, palpitations and pedal edema. This is in concert with previous studies that have also reported dyspnea on exertion as the most common symptom at presentation. Rich et al [14] have reported 60% incidence of dyspnea in patients of pulmonary hypertension, followed by fatigue (19%) and syncope (13%). Mean pulmonary arterial pressure (PSAP) was found to be 69.77±21.2 mmHg in the current study. This was much higher than what has been reported in previous studies. David et al have reported 50.7±13.6 mmHg, Raymond et al have reported 49.5±14.8 mmHg and Rich et al have reported 60±18 mmHg [12, 13, 14]. This observation points towards greater severity of pulmonary hypertension in our study population. The mean pulmonary arterial pressure was found to be higher in men compared to women and this finding was statistically significant with a p-value of 0.016. A mean PSAP of 70.76±22.1 was found in men as against 68.70±20.34 in women. This is in concert with a previous study by Shapiro et al where a mean PSAP of 53±14 mmHg was reported in men and a mean PSAP of 51±14.3 mmHg was reported in women, with a p-value of 0.013 [11].

In the current study, the most common etiology of pulmonary hypertension was found to be Chronic Obstructive Pulmonary Disease (COPD), which was seen in 52.2% of men and 34.4% of women. Incidence of congenital heart disease and valvular heart disease was found to be higher in women. The incidence of primary pulmonary hypertension was also found to be higher in women (7.8%), in the present study. In a previous study, Shapiro et al have also reported a higher incidence of congenital heart disease in women [11]. The etiologies encountered in the current study, differed markedly from those reported earlier in terms of numbers and percentage. Whereas in the current study, the most common etiologies in that order were COPD, valvular heart disease and cardiomyopathies; the most common etiologies reported by ACC/AHA 2009 consensus document on pulmonary hypertension were Chronic thromboembolic pulmonary hypertension, followed by congenital heart disease, portal hypertension and drugs & toxins [16].

CONCLUSION

133 patients presenting with pulmonary hypertension were studied for demographic, clinical, etiological and echocardiographic data. Males outnumbered females, the association between age and NYHA class was found to be statistically significant. The most common symptom at presentation was dyspnea on exertion. The most common etiology was COPD, followed by Valvular heart disease. Sildenafil was found to improve symptoms and exercise capacity.

REFERENCES

[1]. Hoeper MM. Definition, classification, and epidemiology of pulmonary arterial hypertension. Semin Respir Crit Care Med. 2009 Aug;30(4).
[2]. Simonneau G, Galiè N, Rubin LJ, et al. "Clinical classification of pulmonary hypertension". J. Am. Coll. Cardiol.2004. **43** (12 Suppl S): 5S–12S.
[3]. M. Humbert. The burden of pulmonary hypertension. ERJ July 1, 2007 vol. 30 No. 1 1-2.
[4]. A.J. Peacock, N.F. Murphy, J.J.V. McMurray et al. An epidemiological study of pulmonary arterial hypertension. Eur Respir J 2007; 30: 104–109.
[5]. Rich S, Rubin L, Walker AM et al. Anorexigens and pulmonary hypertension in the United States: results from the surveillance of North American pulmonary hypertension. Chest. 2000 Mar;117(3):870-4.
[6]. Denton CP, Black CM. Pulmonary hypertension in systemic sclerosis. Rheum Dis Clin North Am. 2003 May;29(2):335-49, vii.
[7]. Cicalini S, Almodovar S, Grilli E. Pulmonary hypertension and human immunodeficiency virus infection: epidemiology, pathogenesis, and clinical approach. Clin Microbiol Infect. 2011 Jan;17(1):25-33.
[8]. Robalino BD, Moodie DS. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. J Am Coll Cardiol. 1991 Feb;17(2):492-8.
[9]. Gerhard-Paul Diller, Michael A. Gatzoulis. Pulmonary Vascular Disease in Adults With Congenital Heart Disease. Circulation.2007; 115: 1039-1050.
[10]. Selim M. Arcasoy, Jason D. Christie, Victor A et al."Echocardiographic Assessment of Pulmonary Hypertension in Patients with Advanced Lung Disease". American Journal of Respiratory and Critical Care Medicine, Vol. 167, No. 5 (2003), pp. 735-740.
[11]. Shelley Shapiro, Glenna L. Traiger, RN et al. Sex Differences in the Diagnosis, Treatment, and Outcome of Patients With Pulmonary Arterial Hypertension Enrolled in the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management. Chest. 2012;141(2):363-373.

[12]. David B. Badesch, Gary E. RaskobGreg Elliott et al. Pulmonary Arterial Hypertension:Baseline Characteristics From the REVEAL Registry. Chest. 2010;137(2):376-387.

[13]. Raymond L. Benza, Dave P. Miller et al. Predicting Survival in Pulmonary Arterial Hypertension : Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation.2010; 122: 164-172.

[14]. Rich S, Dantzker DR, Ayres SM, Bergofsky EH et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med. 1987 Aug;107(2):216-23.

[15]. Charles D. Burger, Aimee J. Foreman et al. Comparison of Body Habitus in Patients With Pulmonary Arterial Hypertension Enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management With Normative Values From the National Health and Nutrition Examination Survey. Mayo Clin Proc. Feb 2011. 86(2): 105-112.

[16]. Hunt SA, Baker DW, Chin MH et al; for the American College of Cardiology/American Heart Association. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101–2113.