ETIOLOGICAL PATTERNS AND FUNCTIONAL CLASS OF PULMONARY HYPERTENSION IN LUNG DISEASES AT A TERTIARY CARE CENTRE IN INDIA- A PROSPECTIVE STUDY.

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Abstract

Introduction: Pulmonary Hypertension (PH) results from multiple etiological factors, whose natural history varies considerably depending on cause and pathophysiology. The data on the etiological pattern of different lung diseases causing pulmonary hypertension is important because a high index of clinical suspicion can be kept on such patients to detect PH.

Aims: To prospectively evaluate the etiological pattern of pulmonary hypertension among patients with respiratory diseases coming to our centre. We also aimed to evaluate whether etiology is a determinant of functional class in pulmonary hypertension.

Materials and Methods: A prospective observational study of 53 subjects was done. All patients were interviewed about the symptoms and complete physical examination was performed. A baseline echocardiogram was done at the Dept. of Cardiology. All etiologies causing pulmonary hypertension were defined as per predetermined criteria and recorded. Clinical severity assessment was done using WHO- Functional Class, Six minute walk test and echocardiography parameters at the time of presentation. Comparison of the severity parameters were done among the etiologies. The statistical analysis was done using statistical software SPSS Version 16.

Results: In this study, the most common etiology of pulmonary hypertension in lung diseases was Chronic Obstructive Pulmonary Disease(51%) followed by Interstitial lung diseases(22%) and Bronchiectasis (17%). Majority of our patients presented with WHO- Functional class- 3. As part of the severity assessment, COPD patients were found to have a significantly low RVSP (Right Ventricular Systolic Pressure) values when compared to other etiologies. There was no significant difference in six minute walk distance and functional performance among the various etiologies.

Conclusions: In this study, the most common etiology of pulmonary hypertension in lung diseases was Chronic Obstructive Pulmonary
Disease. Most of the patients with Pulmonary Hypertension presented with worse functional performance. COPD patients had a milder pulmonary hypertension when compared to other etiologies.

Introduction:
Pulmonary hypertension is a rare disease with annual incidence of 7 cases per million and a prevalence of 26 to 52 cases per million (Peacock et al, 2007). In a large population based study (Rotterdam study), the estimated prevalence of echocardiographic pulmonary hypertension was 2.6% (Edwardo et al, 2015). An estimated 20 to 25 million people or more suffer from PH of different causes in the developing world (Butrous, 2008) Pulmonary Hypertension (PH) is a hemodynamic and pathophysiological condition defined as an increase in the mean pulmonary arterial pressure >25mmHg at rest as assessed by right heart catheterization (N Galie, 2009). It results from multiple etiological factors, whose natural history varies considerably depending on cause and pathophysiology (Simonneau, 2009).

There are limited studies which have described the epidemiological data on prevalence of various lung diseases causing pulmonary hypertension. None has been done in Indian population till now. This data on the etiological pattern and frequencies of different lung diseases causing pulmonary hypertension is important because a high index of clinical suspicion can be kept on such patients to detect PH early. Recognition of PH in early reversible stages of the disease can help in early initiation of specific treatment. This can at least help in preserving better functional class in such patients.

In our study, we aimed to prospectively evaluate the etiological pattern of pulmonary hypertension among patients with respiratory diseases coming to our centre. We also tested whether etiology plays any role in determining the functional class of pulmonary hypertension in our population.

Subjects and Methods:
This study was conducted at the Department of Pulmonary Medicine, Government Medical College, Trivandrum and Chest Hospital, Calicut from October 2010. The study protocol was approved by the Institutional Ethics Committee of Malabar Institute of Medical Sciences, Calicut. This study was designed as a prospective observational study with study sample of 50 patients.

All patients visiting the respiratory medicine OPD at our institution with pulmonary hypertension (defined as Right Ventricular Systolic Pressure (RVSP)>40mmHg at baseline echocardiogram) due to lung disease (Group 3 of Clinical classification) were included. The lung etiology was determined by specific diagnostic test which is described later. Patient with coexisting comorbidities like cardiac, collagen vascular diseases, thromboembolism) were excluded from the study.

A clinical questionnaire was designed with all the symptoms and signs of pulmonary hypertension and the respiratory symptoms that can be present in each individual patient. All patients were interviewed and physically examined. For each patient, a baseline transthoracic 2D echocardiogram was done at our centre. Right ventricular systolic pressure (RVSP) was estimated which is considered equivalent to pulmonary artery systolic pressure (PASP) in the absence of pulmonary outflow obstruction. Additional information about the causes and consequences of pulmonary hypertension was also recorded.

With Doppler-echocardiography right ventricular systolic pressure (RVSP) was obtained by adding the estimated right atrial pressure (RAP) to the pressure gradient derived from systolic regurgitant tricuspid flow velocity v according the formula: RVSP= 4v^2+ RAP. Echocardiographic estimation of the right atrial pressure was done by measuring the diameter of the inferior vena cava and the respiratory motion of the inferior vena cava (Schannwell, 2007). Theoretically, calculation of mean PAP from PA systolic pressure is possible by equation, mean PAP=0.61×(PA systolic pressure+2 mmHg). This could allow the use of Doppler measurements, applying an accepted definition of PH as mean PAP ≥25 mmHg. According to this a RVSP cut off of 40mmHg was taken, above which the diagnosis of pulmonary hypertension was made.
Indirect signs of pulmonary hypertension such as paradoxical septal motion (septal bowling or flattening), right ventricular systolic dysfunction, pericardial effusion, right ventricular hypertrophy and reduced right ventricular ejection time was also assessed. Other baseline investigations included electrocardiogram, chest X ray and spirometry. Clinical severity assessment at the time of presentation was done using WHO- FUNCTIONAL CLASS (WHO-FC) and Six-minute walk test. The respiratory etiology was defined as per the well accepted standard criteria in clinical practice and has been described in detail elsewhere (GOLD 2017; Bradley 2008; Pasteur 2010)

The statistical analysis in this study was done by descriptive methods (SPSS Version 16). One way ANOVA tests for quantitative variables and Chi-square tests for qualitative variables were used as the tests of significance. A probability value of ‘p’ <0.05 was considered significant. The frequencies of various etiologies were calculated and compared. The various demographic factors, clinical signs and symptoms were compared between the etiologies to detect any significant differences. The assessment of the severity of pulmonary hypertension was done using functional class, RVSP and six minute walk tests and comparison derived among the various etiologies. The relationship between the RVSP values and six minute distances also was studied.

Results:

A total of 53 patients were included in the study. The baseline characteristics of the study population are given in table 1. Dyspnea on exertion was the most common complaint (100%) followed by cough (90%). Loud P2 was seen in majority of the patients (83%) along with pedal oedema and elevated JVP (60% each). The common ECHO findings in the study population are summarized in the table 2.

Chronic obstructive pulmonary disease was the most common etiological factor seen (51%), followed by Interstitial lung diseases (22%) and bronchiectasis (17%). Developmental anomalies of lung were the least common etiology in our study (4%). Table 3 shows the distribution of various clinical characteristics among different etiologies and the level of statistical significance seen. Leg swelling, abdominal distension and giddiness were found to be significantly more (p<0.05) in COPD patients than other patients.

The severity parameters of pulmonary hypertension as measured by RVSP (Right Ventricular Systolic Pressure), six minute walk test and functional class at presentation were compared between the etiologies. The differences in RVSP (in mm Hg), according to the different respiratory etiologies of Pulmonary Hypertension is depicted the box plot in Figure 1. COPD was found to have significantly less baseline RVSP than the non –COPD etiologies (p=0.04).

The severity of pulmonary hypertension was measured using six minute walk test in all patients. The patients with COPD had maximum distance while patients with Bronchiectasis had least values in Six minute walk test. But there was no statistically significant difference. Majority of patients presented in Functional class three (52%) and two (38%). The representation of functional class distribution in each etiology is shown in Figure 2. Among all etiologies Interstitial Lung Disease patients presented with worse functional status. Majority of COPD patients presented in functional class 1 and 2 (87%) indicating a relatively good functional performance. However, this difference was not statistically significant.

Table 1:- Baseline characteristics of the patient population

| Characteristics               | Results                        |
|-------------------------------|--------------------------------|
| Number (N)                    | 53                             |
| Age (median, SD in yrs.)      | 55±13                          |
| Female (%)                    | 19 (36%)                       |
| RVSP mmHg (mean, SD)          | 57.9 ± 11.4                    |
| SMW Distance (m) (mean, SD)   | 300 ± 95.9                     |
| Smokers (%)                   | 13 (24%)                       |
| Alcoholism (%)                | 8(15%)                         |
| Long Term O2 therapy (%)      | 5(10%)                         |

RVSP- Right Ventricular Systolic Pressure, SMW- Six Minute walk
Table 2: Frequency of Echocardiographic findings in Pulmonary Hypertension

| Findings                          | Frequency |
|-----------------------------------|-----------|
| Dilated right atrium, right ventricle | 30(58%)  |
| Paradoxical IVS movement          | 8(15%)    |
| Pericardial effusion              | 3(6%)     |
| Mean RVSP (in mm Hg)              | 57.9±11.4 |

IVS- Inter-ventricular septum, RVSP – Right Ventricular Systolic Pressure

Table 3: Comparison of demographic and clinical parameters among various etiologies

|                       | BRONCHIECTASIS | COPD | ILD | OTHERS | p-VALUE |
|-----------------------|----------------|------|-----|--------|---------|
| Sample size           | 7              | 26   | 11  | 7      |         |
| Age                   | 57.29 ± 8.67   | 51.12 ± 14.32 | 47 ± 12.95 | 61.29 ± 9.96 | 0.105   |
| Female Sex            | 26.3%          | 47.4% | 21.1% | 5.3%   | 0.153   |
| Leg Swelling(Y)       | 20.6%          | 50.0% | 17.6% | 11.8%  | 0.083   |
| Abdominal Distension(Y) | 31.2%      | 50.0% | 6.2%  | 12.5%  | 0.048   |
| Giddiness(Y)          | 7.1%           | 78.6% | 14.3% | 0%     | 0.039   |
| Orthopnea(Y)          | 19.2%          | 42.3% | 26.9% | 11.5%  | 0.408   |
| Smoking(Y)            | 8.7%           | 47.8% | 17.4% | 26.1%  | 0.100   |
| Exposure(Y)           | 16.7%          | 50.0% | 16.7% | 16.7%  | 0.968   |
| Oxygen(Y)             | 40.0%          | 20.0% | 40.0% | 0%     | 0.143   |
| Diuretics(Y)          | 20.0%          | 45.0% | 20.0% | 15.0%  | 0.747   |
| Functional Class(3 &4) | 12.9%       | 48.4% | 29.0% | 9.7%   | 0.343   |
| RVSP                  | 67.57 ± 11.84  | 54.42 ± 12.01 | 59.36 ± 7.487 | 59.29 ± 9.160 | 0.047   |
| SMW distance          | 283 ± 130.97   | 310.13 ± 90.53 | 308 ± 101.163 | 263.33 ± 66.005 | 0.706   |

RVSP: Right Ventricular Systolic Pressure, SMW: Six Minute Walk, Y: Yes

Figure 1: Right Ventricular Systolic Pressure (in mm HG) among different etiologies of Pulmonary Hypertension in lung diseases

1-Bronchiectasis, 2- COPD, 3-ILD, 4- Others
Discussion:
Our study has elucidated the etiological pattern of various lung diseases causing pulmonary hypertension along with the clinical, radiological and echocardiography profile of these patients. The manifestations of pulmonary hypertension are almost often indistinguishable with that of underlying lung disease and development of early pulmonary hypertension often goes unrecognized in these patients. However, early suspicion of pulmonary hypertension in these patients can lead on to initiation of specific treatment and subsequent better outcomes.

The most common etiology among various lung diseases causing pulmonary hypertension was Chronic Obstructive Pulmonary Disease (COPD). Pulmonary hypertension associated with COPD also has significant clinical implications contributing to functional limitation and reduced survival. A study from North America also concluded that COPD was the most common etiology of chronic cor pulmonale (Hyduk A et al, 2005). Also, interestingly, symptoms like leg swelling and abdominal distension showed a significant predominance in COPD patients than in other etiologies (P<.05). Early screening of all COPD patients using echocardiography before clinical evidence of pulmonary hypertension sets in may be therefore useful.

The second most common cause was interstitial lung disease accounting for 22% of all patients. Among the various interstitial lung diseases, connective tissue associated interstitial lung diseases constituted about 63%. These results are similar to previous studies in which most common causes were connective tissue associated interstitial lung disease, sarcoidosis and Idiopathic pulmonary fibrosis (Lettieri CJ et al, 2006). Pulmonary hypertension has significant impact on the outcomes of interstitial lung diseases with an almost three fold increased risk of death (Mathai SC et al, 2009)

Comparison of severity of pulmonary hypertension assessed using RVSP, Six minute walk test and WHO-Functional class among the various etiologies showed a significantly low RVSP (54.42±12.01) in COPD patients (P<.05).This observation is also noted in other studies (Minai OA et al, 2010). COPD patients walked greater distance (mean= 310±90.5 meters) in the six minute walk test and also presented with relatively better functional performance (Functional Class 1& 2).

Conclusion:
COPD is most common among respiratory etiologies to cause pulmonary hypertension. Though majority of patients with respiratory illness presented in WHO-Functional class 3, COPD patients had milder pulmonary hypertension.
Our study reconfirms the role of early cardiac screening using 2DECHO for detection of pulmonary hypertension in COPD patients.

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