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Pulmonary Hypertension in Connective Tissue Disorders: A Trans-thoracic Echocardiographic Study from Eastern India

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Abstract

***Background:** Connective tissue disorders (CTD) like Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) are multi-system diseases with significant mortality and morbidity. Pulmonary artery hypertension (PAH) is one of the under-recognised complications of CTD. While PAH in Systemic Sclerosis (SS) is well documented, the prevalence of PAH in other CTDs is largely under reported, and hence under-treated. This represents a large unmet need in this disease group. The present study was done to generate data on the prevalence of PAH in CTDs in an Eastern Indian population.*

***Materials and methods:** This was a hospital-based single centre observational study. Adult patients with various CTDs, coming to the rheumatology clinic of a tertiary care Medical college were included after proper screening. The CTDs were diagnosed by clinical and laboratory parameters, as per standard criteria. Patients with lung disease and pulmonary valve diseases were excluded. Transthoracic echocardiography with Doppler was done (Vivid 7, GE) to diagnose pulmonary artery hypertension.*

***Results:** There were 162 subjects with CTD in this study with male: female ratio of 41:121. Rheumatoid arthritis was the commonest diagnosis (35%) followed by SLE (28%). Transthoracic echocardiography revealed PAH in 19 subjects (11.7%; 95% CI: 7.6 - 17.6%). The commonest diseases associated with PAH were SS (n = 8) and SLE (n = 8). Titre of anti-nuclear factor was higher in subjects with PAH (compared to those without) for both SS and SLE cases. PAH did not have any correlation with other parameters like ESR, CRP, creatinine, C3 or C4.*

***Conclusion:** More than one in ten subjects with CTD had pulmonary arterial hypertension. However, some CTDs like SS and SLE had much higher prevalence of PAH compared to the other diseases. Disease-specific data on PAH is needed to formulate treatment guidelines.*

***Key words:** Pulmonary hypertension; scleroderma; echocardiography; prevalence; connective tissue diseases.*

Introduction

Connective tissue disorders (CTD) are a heterogeneous group of diseases that affect one or many connective tissues and organs in the body, causing structural and functional disorders[1]. CTDs can be inherited (like Marfan's syndrome) or acquired (mostly autoimmune). For the purpose of this study, the definition of "CTD" is restricted to acquired autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SS), Sjogren's syndrome and other similar multisystem diseases. These diseases may have various complications and pulmonary artery hypertension is one of the under-recognised complications with significant mortality and morbidity.

Pulmonary artery hypertension (PAH) is very rare in the general population but it is more common in certain diseases like CTD (secondary PAH)[2]. Various CTDs may lead to PAH, but the main condition associated with PAH is SS[2]. Life span of patients is significantly shortened in SS-associated PAH with estimated 3 year survival of around 50% in various registries[2]. However, the impact of PAH on disease survival for other CTDs is largely unknown. The exact prevalence of PAH in various other CTDs is not known and it varies with the diagnostic methods used[2]. Studies have found significant differences in prevalence of PAH when pulmonary artery pressure is estimated by echocardiography vis-à-vis cardiac catheterisation. Since CTDs are often associated with lung pathology or independent left heart dysfunction, the true estimation of PAH is often a challenge. PAH is often associated with the presence of other factors like anti-phospholipid antibody or anti-synthetase antibody[2]. Treatment with immunosuppression or immunomodulation may lead to improvement in the PAH in some of these cases[2]. Thus, many cases of CTD-associated PAH may be treatable but under-diagnosis often leads to delay in treatment.

Most of the current knowledge on CTD-associated PAH is derived from registry based data[3]. Such registry may be biased and comparing such data from different countries is

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complicated by lack of uniformity[3]. The gold standard of diagnosis of PAH is right heart catheterisation (RHC) and measurement of pulmonary artery pressure along with capillary wedge pressure[3]. But in the rheumatology unit, it is not often possible to do such an invasive specialised test. Estimation of pulmonary artery pressure by echocardiography is fraught with some fallacies like operator variability, but recent data suggest that there is good correlation between RHC and echocardiography data, provided the TR signal is interpretable[4]. Thus, echocardiography is now a practical, non-invasive alternative to the invasive RHC procedure for clinic-based estimation of the pulmonary artery pressure.

Systemic sclerosis is the main disease for which pulmonary artery hypertension has been researched at length. There are robust data on PAH in SS from various countries, including India[3]. It is a major cause of death in SS and definitive treatments have been shown to reduce pulmonary artery pressure in SS[3]. However, the data for other CTDs like SLE or RA is scarce. Also, the data from various regions of the world are not corroborative. For example, some studies have shown marked difference in prevalence of PAH in CTDs among Asian patients, compared to other parts of the world[3]. A study from China by Hao *et al* (2014) showed that SLE was the major cause of CTD-associated PAH, while SS accounted for only a minority[5]. This is in stark contrast to Western Data where SS accounts for the majority of CTD associated PAH.

Indian data on CTD-associated PAH is grossly inadequate. There are very few disease-specific studies, that too mostly on SS[6]. With the advent of biologic and other therapies, as patients with CTDs are living longer, chronic complications like PAH are becoming more common. This may be a significant cause of morbidity in these patients. Thus, there is an urgent need of data on the prevalence of such complications, especially in non-SS CTDs, in order to understand the unmet needs of these patients and also to allocate health resources. Although Eastern India has a large number of CTD cases, there is almost no data on the prevalence of CTD-PAH in this population.

Aim

The aim of this hospital-based study is to find the prevalence of pulmonary artery hypertension (by non-invasive echocardiography) in a mixed population of connective tissue disorders from Eastern India.

Material and methods

This was a hospital-based cross-sectional observational single-centre study. It was conducted in the Rheumatology clinic of a tertiary care medical college of Eastern India from June 2017 - June 2018. Adult patients (> 12 years) coming to this clinic with various connective tissue disorders were included after proper screening. Diagnosis of the various disorders was done according to the following international criteria:

SLE: SLICC (2012)

Systemic sclerosis (SS): 2013 ACR/EULAR criteria

Rheumatoid arthritis (RA): ACR/EULAR 2010 criteria

Sjögren's syndrome: 2016 ACR/EULAR criteria

Mixed connective tissue disorder (MCTD): Diagnostic criteria according to Alarcón-Segovia and Villareal

Ankylosing spondylitis: ASAS classification criteria, 2009

Dermatomyositis: Bohan and Peter criteria

For others, similar standard criteria were followed.

The study was reviewed and approved by the Institutional ethics committee (MC/Kol/IEC/Non-Spon/565/05-2017). Subjects were chosen by purposive sampling as this suited the busy work schedule of the authors. The chosen subjects were first explained about the study in their native language. Only those who gave written informed consent were included. Demographic details of the study participants were noted and their past medical records were analysed for relevant data. Anti-nuclear Factor (ANF) was done by the qualitative method (Euroimmun: IIFT Mosaic Hep-20-10) using the Eurostar III microscope. ANA profile was done by the sandwich ELISA method (semi-quantitative; Euroimmun Kit). Anti-CCP was also done by Euroimmun kit, but the Quantitative method. Chest X-ray and/or HRCT thorax was done for each subject to rule-out significant lung pathology.

All the echocardiographic measurements were done by the same person for uniformity. Echocardiography with Doppler study was done in Vivid 7 Dimension machine (GE). Only patients who had acceptable trans-thoracic echo window were included in the analysis. Pulmonary artery hypertension was diagnosed by calculating the pulmonary artery systolic pressure (PASP). For this, first the tricuspid regurgitation (TR) gradient was estimated by continuous wave Doppler. Then, to this right atrial pressure is added. For estimating right atrial pressure, the following chart was used:-

- If the inferior vena cava (IVC) is not dilated and there is >50% collapse on inspiration: add 5
- If IVC dilated and > 50% collapse on inspiration: add 10
- If IVC fully dilated and <50% collapse on inspiration: add 15

This estimated RA pressure is added to TR gradient to get

right ventricular systolic pressure. This is considered equivalent to PASP, provided there is no pulmonary valve disease.

PASP measurement was done thrice for each subject and the average of three readings was recorded.

Sample size calculation

There is almost no precedence of a similar study from India. The only other study on CTD-PAH from India had 195 subjects[7]. But that sample size was not based on any statistical principle, but rather was based on convenience sampling, including all available CTD patients in the study period[7]. Since CTD as a group includes various diseases with widely different prevalence of PAH, it is not possible to calculate projected sample size from prevalence data. The sample size for systemic sclerosis will be markedly different from that for SLE. Thus, based on the annual turnover of patients with various CTDs in the rheumatology clinic in our institution, we set a realistic target sample size of 150 for a one year period.

The main exclusion criteria were HIV infection, past or present tuberculosis, known left heart or congenital heart disease, history of smoking, obstructive sleep apnoea, history of intake of drugs or toxins known to affect pulmonary circulation, chronic thromboembolic pulmonary disease (ruled-out by CT pulmonary angiography in suspected cases), portal hypertension and chronic obstructive pulmonary disease. Also, cases with pulmonary stenosis or regurgitation were excluded, due to difficulty in estimating the PASP by echocardiography.

Statistical analysis

The data from the patients was entered into a Microsoft Excel worksheet. Data was entered by one person and cross-checked by another for accuracy. Suitable descriptive and inferential statistical analyses were performed. Categorical data are presented as proportion/percentage and continuous data are presented as mean ± SD. Chi square test was used to calculate significance of difference of proportions. For means of continuous data, student T test was used. $P < 0.05$ was considered significant.

Results

There were a total of 162 subjects in our study. As expected in a study involving rheumatology patients, females were over represented. 121 (74.7%) of the subjects were female. Average age of the subjects was 36.8 ± 13.2 years. The different connective diseases in the subjects are shown in Table I. Rheumatoid arthritis was the most common diagnosis with 35.2% (n = 57) of the subjects having RA. The next most common diagnosis was SLE (27.8%). The average age of RA patients (46.3 ± 11.9 years) was significantly higher than average age of patients with other CTDs (31.6 ± 10.9 years), ($p < 0.001$ by student T test).

Table I: Table showing the diagnoses in the study subjects (n = 162).

Disease	Number	Percentage
Rheumatoid arthritis	57	35.2
Systemic lupus erythematosus	45	27.8
Systemic sclerosis	22	13.6
Ankylosing spondylitis	19	11.7
Psoriatic arthritis	4	2.5
Dermatomyositis	3	1.9
Mixed connective tissue disorder	3	1.9
Juvenile idiopathic arthritis	2	1.2
UCTD, Sjogren's syndrome, Behcet's Disease, CREST syndrome, overlap disease, Takayasu Arteritis, undifferentiated spondyloarthropathy	1 each	

Pulmonary hypertension by echocardiography was found in 19 subjects (11.7%; 95% CI: 7.6 - 17.6%). The male:female ratio was 4:15. However, the occurrence of PAH varied by the underlying disease. Systemic sclerosis was the CTD most associated with PAH. In systemic sclerosis (SS), PAH was found in 36.4% (95% CI: 19.7 - 57%) cases while in SLE, it was found in 17.8% (95% CI: 9.3 - 31.3%). Other than these two diseases, PAH was extremely rare and found only in one case of each of RA, UCTD and Sjogren's syndrome. Overall, PAH was present in 7.9% of non-SS CTD subjects as compared to 36.4% of SS ($p = 0.0009$ by two-tailed Chi square test). All of the SS patients in this study were diffuse Systemic Sclerosis and were Scl-70 positive in all but two cases. Those two cases were anti-RNP and anti-SS-A positive respectively. None of the SS subjects were anti-centromere positive.

In SS cases, Raynaud's phenomenon was present in 90.9% cases and digital ischaemic ulcer/gangrene was present in 54.5% cases. However, there was no correlation of digital ulcers with the presence of PAH.

Fig. 1 compares the various parameters between subjects with PAH and those without. As is seen in that figure, there was no significant difference between the groups in terms of ESR, CRP values or age. Thus, ESR or CRP values did not predict the occurrence of PAH.

In the SS subset, the average age of subjects with PAH (30.8 ± 10.7 years) was lower than those without (36.1 ± 13.4 years) ($p = 0.17$ by student T test). The other parameters like ESR, CRP and serum creatinine were similar between the two groups. Overall ANF was present in high titre (4+)

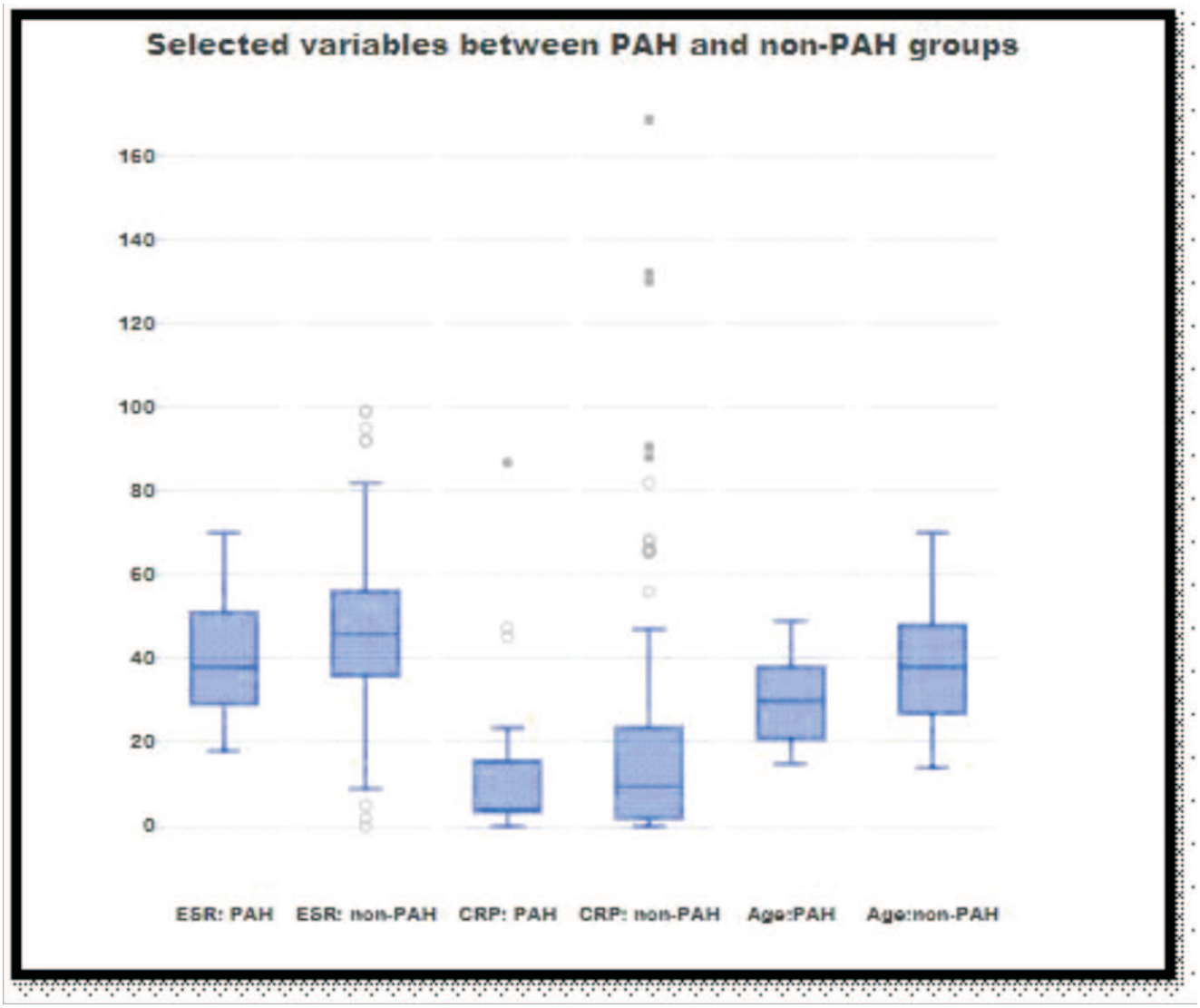

Fig. 1: *Box and Whisker plot showing average ESR, CRP vales and age between subjects with PAH and those without PAH.*

in 40.9% of the subjects with SS. But in the subset with PAH (n = 8), 4+ ANF was found in 50% (n = 4).

In the SLE subset, PAH was found in 17.8% (n = 8). Among the SLE cases without PAH, ANF was strongly positive (4+) in 17 cases (45.9%). But among the PAH positive cases, ANF was strongly positive in 75% (p = 0.24 by chi Square test). Thus, the average titre of ANF was higher in SLE with PAH compared to those without, although the difference did not reach statistical significance, probably due to small number of samples. There was also no significant difference in average C3 (66.5 ± 38.1 vs 56.4 ± 40.3; p = 0.26) or average C4 (17.1 ± 10.1 vs 13.5 ± 8.4; p = 0.15) between PAH and non-PAH subjects with SLE. Anti-phospholipid antibody (APLA) was not done routinely in SLE patients. Only those who had pertinent history (like thrombosis or pregnancy loss) were tested for APLA. Out of 16 SLE patients who were tested for APLA, 4 were positive. 50% of them (n = 2) had pulmonary hypertension. Thus, the numbers were too small to draw any statistical correlation between APLA positivity and PAH.

The average PASP of subjects with PAH was 49 ± 15.7 mm of Hg. There was no significant correlation of PASP with ESR, CRP, creatinine or age (Fig. 2).

Discussion

In this hospital-based study on subjects with connective tissue disease, pulmonary artery hypertension was found in 11.7% of cases. There was no correlation of PASP with inflammatory markers like ESR, CRP, C3 or C4. Among the subjects with PAH, majority had either SLE or systemic sclerosis. Patients with systemic sclerosis had significantly

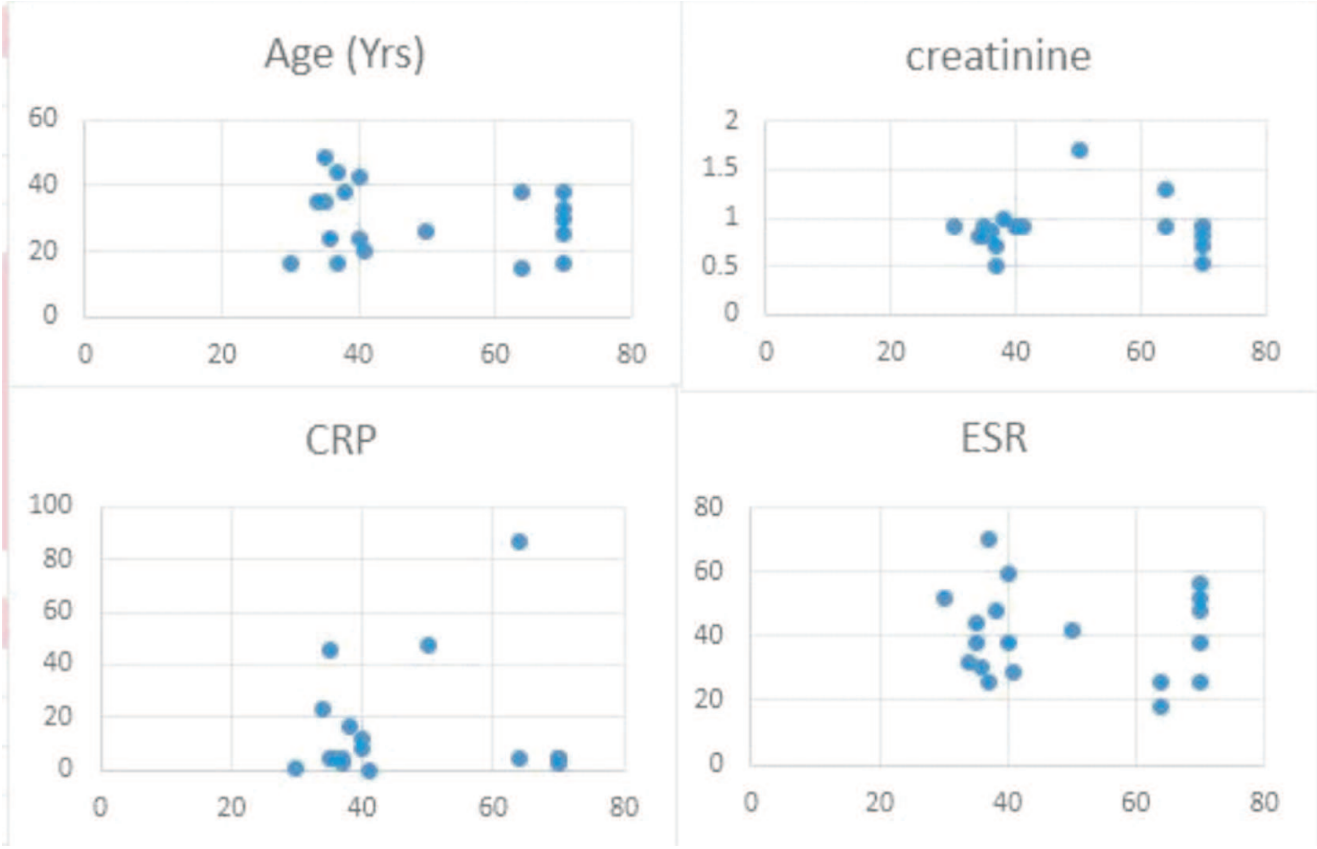

Fig. 2: *X-Y scatter plot showing correlation of PASP (X-axis) with age, ESR, CRP and creatinine values.*

higher prevalence of PAH compared to other CTDs and this PAH in SS occurred at a younger age. In the SLE subset, titre of ANF tended to be higher in subjects with PAH, compared to those without.

The only other similar study on CTD-PAH (echocardiography based) from India was done a decade ago (2009) from Karnataka[7]. In that, Gaude *et al* found the prevalence of PAH to be 14.9%, which is similar to our conclusion[7]. In their study among the CTDs, rheumatoid arthritis was the major entity (61%) followed by SLE (16%). They also found RA to be the commonest diagnosis associated with PAH (13 out of 29; 44.8%). However, in our study, although RA was the most common diagnosis (35.2%), SLE and SS were the commonest diagnoses associated with PAH (42.1% of PAH cases each), while only one case of RA associated PAH was found. Gaude *et al* found PAH to be associated with polymyositis, MCTD and Ankylosing spondylitis in some cases. In our study, except for the above mentioned diseases, the only other diseases associated with PAH were UCTD and Sjogren's syndrome. In our study, among the SS cases, PAH was found in 36.4%, while in the Karnataka study, it was 58%[7].

A study on CTD-associated PAH, as diagnosed by RHC, was done recently in China[5]. In it, it was seen that SLE, followed by Sjogren's syndrome were the main CTDs associated with PAH[5]. The prevalence of PAH in SLE patients varies from country to country[3]. While in Caucasians, the prevalence is reported at 8 - 17%, for other regions, the prevalence of PAH is reported to be as high as 49%[3]. A study from USA found that PAH prevalence increased from 14% to 43% over 5 years in a cohort of patients with SLE[8]. The method used for diagnosis of PAH (invasive vs. non-invasive) also affects the prevalence data. In our present study, PAH was found in 17.8% of SLE cases. In the aforementioned study from Karnataka (also echocardiography based), SLE-associated PAH was found in 9.4%[7]. There are certain predictors of PAH in SLE like Raynaud's phenomenon, active renal disease, vasculitis manifestations and presence of anti-U1-RNP or anti-Phospholipid antibodies[9]. In our study, the average titre of ANF in SLE cases was found to be higher in those with PAH compared to those without. However, C3, C4 or creatinine levels were similar and Raynaud's phenomenon was not documented.

The pathophysiology of PAH in CTDs is still largely unknown, but it is likely to be a multi-factorial process[3]. Some of the putative mechanisms are mutations in the BMPR2 pathway, anti-endothelial antibodies, impaired T-cell regulator activity

and angiogenesis[3]. In systemic sclerosis, there is progressive remodelling of small-to-medium sized pulmonary vasculature[10]. Decrease in Nitric oxide in pulmonary vessels, increase in serotonin mediated vasoconstriction and intra-luminal micro-thrombosis are some of the possible pathophysiologic pathways in SS-PAH[10]. In SLE, increased serum levels of endothelin-1 and thromboxane-A2 and certain auto-antibodies are possible factors in PAH[9]. Like SS, microthrombi may be a secondary event aggravating the PAH[9]. Genetic factors also play an important role in the process[10]. In SS, transcriptomics from peripheral blood mononuclear cells showed significant alterations in certain gene expressions, including those for angiogenesis[11]. However, the exact role of genes in CTD-PAH is still obscure.

A recent systematic review was conducted by Yang *et al* on the prevalence of PAH in CTDs[12]. In that review, it was seen that the majority of studies focussed only on SS[12]. The pooled prevalence of PAH was 13% (95% CI: 9.2 - 18.2%) but this figure varied widely by the specific diseases. For SS, the pooled prevalence was 13% while for SLE, it was 3.3%[12]. Also, when RHC was done, the prevalence of SS-PAH was 8.2%, while for echocardiographic studies, it was 18%[12]. The few Indian studies that have been done to date on CTD-PAH are all echocardiography based[3]. Thus, whether the prevalence data in Indian population will vary with RHC-based estimations is still unknown.

Most of the studies of CTD-PAH have been done in institutional setting, like the present one, due to easy access to a large patient pool. In a community based study, it was seen that 26.7% of cases had PAH[13]. But that study only involved patients with SS and MCTD[13]. Also, in a community setting, echocardiography is the only feasible option for the estimation of PAH and this may over-estimate the pulmonary pressure in many cases. Thus, the data on PAH in CTD is still lacking in many cases and uniform studies involving a wide range of different diseases are still absent.

Management of CTD-PAH is still an area of active research. Immunomodulatory therapy for the underlying disease may help in some cases, along with supportive measures like oxygen and correction of anaemia[3]. Newer options like endothelin antagonist and phosphodiesterase inhibitors have also been used with some success[14]. Prostaglandin analogues like epoprostenol have also been shown to improve pulmonary haemodynamics in SS-PAH[15]. However, there are still concerns about its safety.

The main strength of the present study is inclusion of a wide variety of connective tissue disorders. This gives a fair idea of the prevalence of PAH in various CTDs in our population. The main limitations of the present study is the lack of RHC data. But such invasive investigations are not always feasible in the rheumatology unit.

Conclusion

Pulmonary artery hypertension was present in 1 in 9 cases of connective tissue disorders. Systemic sclerosis and systemic lupus were the two main diseases associated with PAH. Further studies, especially those involving right heart catheterisation, are needed to elucidate the prevalence of CTD-PAH in the Indian population.

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