Original research article

A Prospective Study to Measure Pulmonary Artery Hypertension Using Two-Dimensional Echocardiography in Thyroid Dysfunction

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Abstract

Aim: To evaluate the two-dimensional echocardiographic assessment of pulmonary artery hypertension in thyroid dysfunction.

Methods: A prospective double blind randomized controlled study was conducted at ARC Hospital, Bhagalpur, Bihar, India for 1 year. Thyroid function tests were done in all cases using Enzyme immunoassay to confirm the presence of hypo or hyperthyroidism. Electrocardiography was recorded in all the patients. Chest X-rays were done and examined for roentgenographic signs of pulmonary hypertension, i.e. right descending pulmonary artery diameter of >1.5 cm. 2D-Echocardiography was done in all cases and screened for the presence and severity of pulmonary hypertension.

Results: In our study out of the 100 cases, 70(70%) cases were of Hypothyroidism and 30 (30%) cases were of Hyperthyroidism. Unpaired t test is applied. P value is significant if < 0.05 PASP value in patients with hyperthyroidism was 31.06mm Hg while that in the patients with hypothyroidism was 27.17mm Hg. Difference between them was comparable. 80% patients with hypothyroidism and 66.66% patients with hyperthyroidism had normal PASP level. While 20% patients with hyperthyroidism had mild and moderate PASP each, only 16.67% with hypothyroidism had mild PASP. The mean PASP by Doppler Echocardiography was 39.52 mm of Hg in the pre-treatment group. And the mean PASP during the follow up (after 10 months) was 31 mm of Hg. Among the patients in the Hypothyroidism group with PAH, the pre-treatment values of TSH and PASP were high and reduced in the follow-up (after 10 months of treatment) Among the patients in the Hyperthyroidism group with PAH, the mean pre-treatment value of TSH was 0.2 and increased to 2.35 in the follow up. Mean PASP value was 42.6 and reduced in the follow-up (after 10 months of treatment) to 31.7.

Conclusion: The PAH secondary to thyroid dysfunctions may be reversed by restoration of euthyroid state, and hence patients have a good prognosis if diagnosed and treated timely. So every patient of thyroid dysfunction should be screened for PAH, even though further studies are needed to substantiate this.

Keywords: thyroid dysfunctions, PAH, Doppler Echocardiography

Introduction

Pulmonary hypertension (PH) is a hemodynamic and pathological state with a high rate of mortality that may lead to right heart failure and ultimately death if untreated. PH can be found

in multiple clinical conditions and its symptoms are nonspecific. Badesch et al.[1] brought attention to the relationship between PH and hypothyroidism and growing evidences confirmed the association between PH and thyroid diseases thereafter. Curnock et al.[2] revealed in their retrospective study that the prevalence of hypothyroidism in 41 patients with PH was 22.5%. Chu et al.[3] found that the prevalence of autoimmune thyroid disease in the patients with PH was 49%. In another study, the prevalence of thyroid disease was 24% in PH patients and 15% in the control group.[4] On the other hand, patients with thyroid disease, predominantly hyperthyroidism, also have higher pulmonary arterial pressure than healthy subjects. The prevalence of PH among patients with hyperthyroidism was reported to be 34-65%.[5]

Thyroid hormones may play an important role in regulating PASP. However, the association of thyroid hormones with PH remains controversial. Marvisi et al.[6] demonstrated that in population with recently diagnosed hyperthyroidism without antithyroid treatment, PASP was associated with thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) levels. However, Sugiura et al.[7] showed that PASP was not significantly correlated with free triiodothyronine (FT_3) or FT_4 in patients with Graves' disease. And in patients with Hashimoto's thyroiditis, it was shown that FT_3, FT_4, or TSH was not independently related to PASP.[8,9] Meanwhile, PASP is considered as an important prognostic factor for assessing morbidity and mortality in patients with CAD; thus, it is essential to find out the potential risk factors for PH in CAD patients. According to previous studies, it is acknowledged that thyroid dysfunction could induce PH via multiple pathways, but whether thyroid hormones within reference range would affect PASP is still uncertain.

Materials and Methods

A prospective double blind randomized controlled study was conducted in the Department of Consultant Physician and Cardiologist, ARC Hospital, Bhagalpur, Bihar, India for 1 year. after taking the approval of the protocol review committee and institutional ethics committee.

Thyroid function tests were done in all cases using Enzyme immunoassay to confirm the presence of hypoor hyperthyroidism. Electrocardiography was recorded in all the patients. Chest X-rays were done and examined for roentgenographic signs of pulmonary hypertension, i.e. right descending pulmonary artery diameter of >1.5 cm. 2D-Echocardiography was done in all cases and screened for the presence and severity of pulmonary hypertension. Right ventricular systolic pressure was calculated from the pressure gradient between the right ventricle and atrium measured by continuous wave Doppler echocardiography according to standard techniques. CVP was not elevated on clinical examination and therefore assumed to be 5 mmHg. Mean right atrial pressure is equivalent to CVP. PASP was calculated byadding up RAP and RVSP. Patients with PASP of >30 mmHg were treated for the underlying hypothyroidism (thyroxine) and hyperthyroidism (Carbimazole) and reassessed after a period of 10 months with 2D-Echocardiography for thereduction in PASP.

Inclusion Criteria

- Patients with hypo/hyperthyroidism.
- Patients more than 18 years of age, both maleand female
- Patients willing to participate in the study

Exclusion Criteria

- Clinical features of chronic pulmonary diseaseslike COAD, interstitial lung disease
- Known cases of connective tissue diseases.

- Underlying cardiac diseases like VSD,cardiomyopathies, myocarditis etc.
- Chronic liver disease or cirrhosis.
- Chronic hypoxemia.
- Patients on treatment for thyroid disorders for more than 6 months.

Results

Table 1: Distribution of cases in hypothyroidism and hyperthyroidism

	Hypothyroidism	**Hyperthyroidism**	**Total**
Number of cases	70	30	100

In our study out of the 100 cases, 70(70%) cases were of Hypothyroidism and 30 (30%) cases were ofHyperthyroidism.

Table 2: Distribution of mean PASP using 2D-ECHO

Variable	Mean± sd	Mean± Sd	**p-value**
	Hypothyroidism	Hyperthyroidism	
2D-ECHO PASP(RVSP+RA)	27.17±4.89	31.06±10.87	0.07

Unpaired t test is applied. P value is significant if < 0.05 PASP value in patients with hyperthyroidism was 31.06mm Hg while that in the patients with hypothyroidism was 27.17mm Hg. Difference between them was comparable.

Table 3: Comparison of PASP in Hypothyroidism and Hyperthyroidism

PASP GROUP	**Thyroid status**				TOTAL
	Hypothyroidism		Hyperthyroidism		
	N	**%**	**N**	**%**	
Normal (PASP≤ 30 mm Hg)	56	80	20	66.66	76
Mild (PASP 31 to 45 mm Hg)	14	20	5	16.67	19
Moderate (PASP 46 to 60 mm Hg)	0	-	5	16.67	5
Severe (PASP>60 mm Hg)	0	-	0	0	
Grand Total	**70**	**70**	**30**	**30**	**100**

80% patients with hypothyroidism and 66.66% patients with hyperthyroidism had normal PASP level. While 20% patients with hyperthyroidism had mild and moderate PASP each, only 16.67% with hypothyroidism had mild PASP.

Table 4: Comparison of PASP in the follow up group: pre-treatment and post treatment

Parameter	Mean± SD		
	Before	After	P value
2D-ECHO PASP mm Hg	39.52±5.06	31±5.28	0.001

The mean PASP by Doppler Echocardiography was 39.52 mm of Hg in the pre-treatment group. And the mean PASPduring the follow up (after 10 months) was 31 mm of Hg.

Table 5: Comparison of TSH, T3, T4 and PASP among patients of Hypothyroidism in the follow up group, pre and post

Variable	Mean± SD		P value
	Before	After	
TSH (uIU/ml)	17.02±9.87	3.22±2.03	0.01
T3 (ng/ml)	0.71±0.22	1.25±0.54	0.04
T4 (ug/dl)	5.54±3.02	8.06±1.75	0.003
2D-ECHO PASP mm Hg	35.95±3.55	30.58±6.1	0.007

Among the patients in the Hypothyroidism group with PAH, the pre-treatment values of TSH and PASP were high andreduced in the follow-up (after 10 months of treatment)

Table 6: Comparison of TSH, T3, T4 and PASP among patients of Hyperthyroidism in the follow up group, pre and post treatment

Variable	Hyperthyroidism (Mean± SD)		P value
	Before	After follow up	
TSH (uIU/ml)	0.2±0.05	2.35±1.77	0.06
T3 (ng/ml)	2.7±0.62	1.22±0.25	0.021
T4 (ug/dl)	17.03±3.12	9.13±1.04	0.011
2D-ECHO PASP mm Hg	42.6±6.25	31.7±4.95	0.024

Among the patients in the Hyperthyroidism group with PAH, the mean pre-treatment value of TSH was 0.2 and increased to 2.35 in the follow up. Mean PASP value was 42.6 and reduced in the follow-up (after 10 months oftreatment) to 31.7.

Discussion

Several studies have shown associations between thyroid disease and pulmonary hypertension. In PAH there is asustained increase in pulmonary artery pressure and a progressive increase in pulmonary vascular resistance, which leads to right ventricular insufficiency and oftenpremature death. Mean pulmonary artery pressure (MPAP), under physiological conditions and at sea level, is < 20 mmHg, and pulmonary artery systolic pressure(PASP) is < 30 mmHg.

In a study by Marvisi M et al., prevalence of PAH in recently diagnosed hyperthyroids was found to be 35% [10] while in his other study, involving 114 patients with hyperthyroidism (47 with Graves' disease and 67 with multinodular goiter), the prevalence of PAH was 43%.[11]Here PASP, as estimated by echocardiography, was > 30 mmHg. In a study by Mercé J et al. of 39 patients recently diagnosed with hyperthyroidism, the prevalence of PAH (PASP> 35mm Hg) was found to be 41%.[12] In a retrospective study by Curnock AL et al., theprevalence of hypothyroidism in 41 patients with PAHwas found to be 22.5% which was higher than the incidence that we found in our study.[13] In a study by Li JH et al., 356 patients having PAH and 698 controls not having PAH were retrospectively evaluated. Of thepatients with PAH, thyroid disease was present in 85 patients(24%), and 107 (15%) in controls.[14] In our studyPASP in hyperthyroidism was 31.06mm while hypothyroidism was 27.17. Difference between them was comparable. 20% patients with hyperthyroidism had mild PASP and whereas 16.67% with hypothyroidism had mild to moderate PASP. Our

finding on PASP is on the line with published studies. The mean PASP by Doppler Echocardiography was 39.52 mm of Hg in the pre-treatment group. And the mean PASP during the follow up (after 10 months) was 31 mm of Hg.
Mean TSH, T3, T4 and PASP (pre-treatment) values among the follow up patients were 17.02±9.87, 0.71±0.22, 5.54±3.02 and 35.95±3.55, respectively in the hypothyroidism group. Post- treatment values of Mean TSH, T3, T4 and PASP were3.22±2.03, 1.25±0.54, 8.06±1.75 and 30.58±6.1.

Mean TSH value was decreased after 10 months offollow up while values of T3 and T4 had increased after 10 months of follow up. Mean PASP value also decreased in the follow up after 10 months following treatment.

Mean TSH, T3, T4 and PASP (pre-treatment) values among the follow up patients were 0.2±0.05, 2.7±0.62, 17.03±3.12 and 42.6±6.25 respectively in the hyperthyroidism group. Post- treatment values of Mean TSH, T3, T4 and PASP were 2.35±1.77, 1.22±0.25, 9.13±1.04 and 31.7±4.95 Mean TSH value was increased after 10 months of follow up while values of T3 and T4 had decreased after 10 months of follow up. Mean PASP values also decreased in the follow up after 10 months following treatment. The change in PASP after the treatment wascomparable with the findings of other studies. In a study by Thurnheer R et al. in 1997[15], in 4 hyperthyroid cases mean pre-treatment PASP was 40 ± 11 mmHg which decreased to 25 ± 6 mmHg after treatment with radioactive iodine or ethionamides. In an observational study by Marvisi M et al.[10] in 34hyperthyroid patients (17 without treatment; 17 treatedwith methimazole; control group 17), mild pulmonary hypertension was present in 35% of the patients in the untreated hyperthyroid group (mean PASP of 28.88 ± 6.41 mmHg) and in none of the patients of the other groups.

In other study by Marvisi M et al.[11], the role ofmethimazole in the regulation of pulmonary vascular resistance in hyperthyroid patients with PAH was studied After treatment for a period of 15 days, PASPvalues in the methimazole group decreased from a valueof 34.3 ± 3.2 mmHg to 29.2 ± 3.3 mmHg, compared tothe partial thyroidectomy group, where decrease wasfrom 34.3 ± 3.0 mmHg to 34.1 ± 2.9 mmHg ($p< 0.001$). Methimazole's role in regulating production of N(G)-nitro-L-arginine methyl ester (L-NAME), anarginine analogue, producing acute NO synthesis inhibition has been shown in some studies.

In literature, the etiology of strong relationshipbetween thyroid disease and pulmonary hypertension remains unclear. One possible explanation is that increased total blood volume contributes to increased pulmonary blood flow and pulmonary vascular resistance. Another possibility is the direct effect of thyroid hormones on the pulmonary vasculature. This theory is supported by, the reversible change of pulmonary hypertension seen after successful treatment of hyperthyroidism. The mechanisms include an increase in metabolism of intrinsic pulmonary vasodilating substances and a decrease in vasoconstrictor metabolism. Besides the effect of an excess of thyroid hormones, systemic auto antibodies may also play a role in pulmonary vascular endothelium injury and lead topulmonary hypertension.

Conclusion

The PAH secondary to thyroid dysfunctions may be reversed by restoration of euthyroid state, and hence patients have a good prognosis if diagnosed and treated timely. So every patient of thyroid dysfunction should bescreened for PAH, even though further studies are needed to substantiate this.

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