

# Assessment of Thyroid Function in Idiopathic Pulmonary Hypertension

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## Abstract

**Background:** Idiopathic pulmonary hypertension (IPAH) is a rare, debilitating, and fatal disease. Late-onset treatment can lead to right heart failure, multiple organ damage, and death. Since the thyroid plays a major role in the metabolism and hemodynamics in humans, the screening of thyroid function is crucial. Thyroid dysfunction has been reported to cause pulmonary hypertension, but the thyroid is also involved in IPAH.

**Objectives:** The aim of this study was to evaluate thyroid function in IPAH patients.

**Patients and Methods:** Fifty-three IPAH patients aged 16 - 75 years-old were enrolled in this cross sectional study, and their right ventricular functions, hemodynamics, and six minute walk tests (SMWTs) were evaluated. Thyroid function tests were conducted, and their associations with the patients' pulmonary arterial pressures (PAPs) and functional capacities were assessed. The data were analyzed using the SPSS 15 statistical software.

**Results:** In this research, 84.8% of the participants were women. The mean PAP was 51.6 mmHg (31-87) and mean thyroid stimulating hormone (TSH) level was 4.2 mIU/ml (0.7 - 10). Subclinical hypothyroidism was detected in 26 patients (49.1%). There were significant correlations of the TSH level with the right ventricular (RV) end diastolic dimension (P value = 0.05) and triiodothyronine (T3) with the tricuspid annular plane systolic excursion (TAPSE) (P value = 0.04), an inverse relationship between the SMWT and the TSH level (P value = 0.004), but no significant relationship between these parameters and the thyroxine (T4) level.

**Conclusions:** IPAH is associated with subclinical hypothyroidism and low patient functional capacity, and is more common in RV failure.

**Keywords:** Idiopathic Pulmonary Arterial Hypertension (IPAH), Thyroid Dysfunction

## 1. Background

Pulmonary hypertension is a complex, multidisciplinary disorder defined as an increase in the mean pulmonary arterial pressure (mPAP) of 25 mmHg at rest, assessed by right heart catheterization (RHC) (1). It refers to the presence of high pulmonary vascular resistance, and can be the end result of a variety of different underlying disorders (2). It is not very common, but with the new developments taking place in diagnostic and management techniques, pulmonary arterial hypertension (PAH) patients are identified earlier every day. PAH is more common in women (1.7:1) with a mean age of 36 years, (3) and chronic right ventricular (RV) pressure overload and RV failure can lead to end-stage organ damage (including the kidneys, liver, and thyroid gland (4)), as well as many other hemodynamic changes that could be fatal. Early diagnosis and management can be critical and lifesaving in such cases.

Idiopathic PAH is a rare disease of unknown etiology, which can be confirmed when no significant heart disease, lung disease, or pulmonary thromboembolism (PTE) is found, and the pulmonary capillary wedge pressure (PCWP) is less than 15 mmHg (5).

The thyroid is an important organ, with many metabolic and hemodynamic effects, and several cases of PAH have been reported in hypo and hyperthyroid disorders (3, 6). Thyroid function can also be affected in idiopathic pulmonary arterial hypertension (IPAH) and RV dysfunction. Therefore, measuring the level of the thyroid stimulating hormone (TSH) is a useful marker in screening thyroid function (7).

## 2. Objectives

In this study, we evaluated thyroid function in IPAH patients, and its relationship to the RV function, hemodynamic parameters, and a patient's functional capacity.

## 3. Patients and Methods

This single center case series study was conducted in the Cardiology Department at the Imam Reza Medical and Research Center in Mashhad, Iran, from August of 2013 until September of 2014, and enrolled a total of 53

consecutive IPAH patients (mean age of 39 years old, consisting of 84.9% females). The diagnosis was confirmed by right heart catheterization (RHC) (Swan or A1 catheter), after the complete evaluation of each patient by a single, well-trained cardiologist and a pulmonologist in PAH, by excluding the other etiologies for this condition. The evaluation of RV dysfunction was done by both a thorough physical examination and echocardiographic examination using a 2 MHz GE S4 Probe by a single cardiologist. The thyroid markers (TSH, thyroxine [T4], and triiodothyronine [T3]) were assessed by electrochemiluminescence using Roche kits in the Imam Resa Laboratory. The functional capacity was studied using the (SMWT) in the rehabilitation clinic.

Those patients with lung, liver, and renal disease, congenital and structural heart disease, cancer, rheumatological disorders, thalassemia and overt clinical thyroid disorders, or on iodine or amiodarone treatment were excluded from the study.

### 3.1. Statistical Analysis

The continuous variables were expressed as the mean  $\pm$  SD, independent groups were compared using the unpaired Student's t-test or Mann-Whitney U test. Statistical analyses were performed using SPSS 15 for Windows (SPSS Inc., Chicago, IL, USA), and statistical significance was defined at  $P < 0.05$ .

## 4. Results

The baseline characteristics of the patient population are shown in Table 1. In addition, the comparisons of the thyroid hormones levels with the echocardiographic, hemodynamic, and functional parameters are presented in Table 2, in detail.

**Table 1.** Baseline Characteristics of the Studied Patients (n=33)

	Minimum	Maximum	Mean $\pm$ SD
<b>TSH, mIU/ml</b>	0.7	10	4.2 $\pm$ 2.1
<b>T3, n/dl</b>	73	210	124.3 $\pm$ 23.9
<b>T4, mcg/dl</b>	6	12	8.7 $\pm$ 1.5
<b>RVEDD, cm</b>	2.5	5.9	3.8 $\pm$ 0.79
<b>TAPSE, mm</b>	0.9	3.1	1.8 $\pm$ 0.4
<b>Mean PAP, mmHg</b>	31	87	51.6 $\pm$ 11.4
<b>CVP, mmHg</b>	3	28	9.9 $\pm$ 4.4
<b>CO, L/min</b>	2.1	7	4.1 $\pm$ 1.1
<b>SMWT, m</b>	115	525	369.5 $\pm$ 107.4
<b>Age, y</b>	16	75	39.1 $\pm$ 13.2

**Table 2.** Comparisons of Thyroid Hormone Levels With Echocardiographic, Hemodynamic, and Functional Parameters (n=53)

	TSH, mIU/ml	T3, ng/dl	T4, mcg/dl
<b>TAPSE</b>			
$\geq 15$ , mm	4	128	8.8
$< 15$ , mm	4.9	114.5	8.6
P Value	.06	.04	.4
<b>RVEDD</b>			
$\geq 3$ , cm	4.4	120.8	8.6
$< 3$ , cm	3	123.8	9.8
P Value	.05	.3	.1
<b>CO</b>			
$\geq 4$ , L/min	3.9	127.5	8.9
$< 4$ , L/min	4.7	120	8.6
P Value	.2	.5	.5
<b>CVP</b>			
$\geq 5$ , mmHg	4.3	124	8.6
$< 5$ , mmHg	3.7	129.3	10.3
P Value	.4	.13	.06
<b>SMWT</b>			
$\geq 400$ , m	3.5	129.6	8.9
$< 400$ , m	5.1	118.5	8.5
P Value	.004	.2	.25
<b>SMWT</b>			
$\geq 200$ , m	5	120.3	8.9
$< 200$ , m	6.2	98	8.5
P Value	.02	.03	.02

The mean TSH level of the TAPSE < 15 mm was 4.9, and TAPSE  $\geq$  15 mm was 4 ( $P = 0.06$ ); of the RVEDD > 30 mm was 4.4, and RVEDD < 30 mm was 3 ( $P = 0.05$ ); and in the 6 mw test < 400 meters it was 5.1, and in the 6 mw test > 400 meters it was 3.5 ( $P = 0.004$ ). Moreover, the mean sys PAP was 80.7 mmHg (45 - 135) in the TSH  $\geq$  4 mIU/ml and 70.4 mmHg (45 - 130) in the TSH < 4 ( $P = 0.09$ ). Furthermore, the mean T3 level in the TAPSE < 15 mm was 114.5 and 128.5 in the TAPSE  $\geq$  15 mm ( $P = 0.048$ ); it was 98 in the 6 mw test < 200 meters and 120.5 in the 6 mw test > 200 meters ( $P = 0.03$ ). However, no significant relationships were revealed between the T4 level and the hemodynamic and echocardiographic parameters.

## 5. Discussion

In total, 53 patients with a mean age of 39.1 years old, consisting of 85% women, were enrolled in this study. As described in the previous literature on IPAH, the mean age was 35-55 years old (2, 3). Their thyroid functions were evaluated: the mean TSH level was 4.2 mIU/ml (49% had a TSH level over 4), mean T3 level was 124.3 ng/dl, and mean T4 level was 8.7 mcg/dl, which are all within the normal range. Therefore, this condition could be defined as subclinical hypothyroidism in nearly half of the patients.

The means of the TAPSE and RVEDD were 1.8 and 3.8 cm, respectively, which implies an increased RV size and reduced function in most patients. Moreover, the mean CVP was 9.9 mmHg (slightly elevated), and the mean CO was 4.1 L/kg/min (in the normal range). Overall, 67.5% of the patients had New York Heart Association (NYHA) classifications of II or III, which was similar to other studies.

There were no significant relationships with regard to age, sex, or TSH level, and no meaningful correlation was found between the mean PAP and thyroid parameters. However, an increase in the TSH level was found to be significantly related to an increase in the RVEDD ( $P$  value < 0.05) and reduced T3 levels were seen in relation to the TAPSE values of less than 15 ( $P$  value < 0.04). Moreover, the hemodynamic indicators, such as the CVP, mean PAP, and CO, showed no correlation with the thyroid parameters. With regard to the functional capacity, a significant relationship was achieved between the SMWTs of less than 200 m, and the TSH, T4, and T3 levels ( $P$  value < 0.02, 0.02, and 0.03, respectively).

The thyroid is one of the most important organs involved in the hemodynamics of the human body (8, 9). Associations between thyroid disorders (“hypo” or “hyper”) and pulmonary hypertension have been reported in many cases, (10) and treatment leads to the modification of pulmonary hypertension (11, 12). There have been few studies that have evaluated thyroid function in IPAH. Since subclinical hypothyroidism can be seen in chronic diseases like heart failure, (13) RV failure in IPAH can contribute to increased TSH levels (14) and low functional capacity in these patients. Immunological disorders can sometimes be the cause for thyroid disease, and “auto-

antibodies” can also contribute to the physiological pathway of PAH in these patients (7, 15).

Altogether, subclinical hypothyroidism has been confirmed in nearly 50% of the PAH patients in correlation with the RVEDD, TAPSE, and patients’ limited functional capacity. Since these parameters are important markers in the disease prognosis, one can conclude that in significant PAH and RV failure, subclinical hypothyroidism may be present, which can affect the impaired functional capacity. In this study, the significant relationship shown between the hemodynamic parameters and NYHA class could have been due to the limited number of patients in NYHA class IV, and severe RV failure. Accordingly, impaired thyroid function is most often related to, and a consequence of, RV failure, and not exactly due to PAH.

The routine checking of thyroid tests is recommended for PAH patients, especially those in RV failure (which could be the cause of low functional capacity). Whether or not the treatment of hypothyroidism can improve PAH symptoms should be evaluated in further trials.

### 5.1. Limitations

Although this study did not use them, it is better to evaluate RV function with tissue Doppler imaging and cardiac MRIs. Following up the patients with regard to their clinical outcomes could also improve the validity of the achieved data.

### 5.2. Conclusion

Subclinical hypothyroidism can be seen in IPAH patients with relation to an increased RV size, reduced TAPSE, limited functional capacity, and a poor prognosis; however, it shows no relationship with the mean PAP and hemodynamic parameters. Whether or not treatment using thyroid hormones can be beneficial in this respect should be investigated in future studies.

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## Footnotes

**Authors’ Contribution:** Study concept and design: Farveh Vakilian; acquisition of data: Maysam Shegofta and Farveh Vakilian; analysis and interpretation of data: Shahrzad M Lari and Farveh Vakilian, Sahar Ghare; drafting of the manuscript: Maysam Shegofta and Farveh Vakilian; critical revision of the manuscript for important intellectual content: Davod Attaran; statistical analysis: Shahrzad M Lari; administrative, technical, and material support: Davod Attaran; study supervision: Davod Attaran and Farveh Vakilian; endocrine consults about thyroid: Sahar Ghare.

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