Clinical Utility of Thyroperoxidase Antibody Testing in Patients with Pulmonary Hypertension

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Abstract. ***Background:*** The association of autoimmune thyroid disease (AITD) in patients with pulmonary arterial hypertension (PAH) has been well-recognized, yet the best method to screen for thyroid disease is unclear. Since there may be an underlying common immunopathologic link, we sought to determine whether testing for thyroperoxidase antibody (TPOAb) would be a useful screening tool for AITD in PAH. ***Methods:*** This retrospective study comprised 101 consecutive PAH patients seen at Mayo Clinic Jacksonville's Pulmonary Hypertension Center from 2001 to 2008 who fulfilled two requirements: they met the WHO criteria for PAH, and they had measurements of TPOAb levels and thyroid stimulating hormone (TSH). ***Results:*** Of the 101 patients in the cohort, 37 met criteria for AITD. Two patients had an elevated level of TPOAb in the setting of a normal TSH and not taking thyroid hormone medication. TPOAb sensitivity was 46% (95% confidence interval [CI], 29 to 63%), specificity 97% (95% CI 89 to 99%), positive predictive value (PPV) was 89% (95% CI 67 to 98%), and negative predictive value (NPV) was 76% (95% CI 65 to 84%). ***Conclusions:*** Many patients with PAH have a concomitant thyroid disorder. Screening for TPOAb revealed elevated levels in approximately half of those with AITD and PAH. However, TPOAb was elevated in only 2 patients with both a normal TSH and no prior diagnosis of thyroid disease. The low sensitivity of TPOAb demonstrates limited value as a screening test for thyroid disease compared to a medical history and a measurement of TSH.

Keywords. Thyroperoxidase • Antibody • Pulmonary hypertension • Thyroid • Autoimmune

Introduction

Thyroid thyroperoxidase antibodies (TPOAb) are circulating immunoglobulins directed against a component of the smooth endoplasmic reticulum of thyroid cells.[1] Detectable levels of TPOAbs are mainly associated with thyroid autoimmune disorders and thyroid cancers. However, a greater frequency of elevated levels has been found in a host of other systemic diseases. The diseases include rheumatoid arthritis, myasthenia gravis, diabetes mellitus, systemic lupus erythematosus, biliary cirrhosis, mixed connective tissue disease, Sjögren's syndrome, Addison's disease, and pernicious anemia.[2,3,4,5,6] To date, no direct pathological role has been definitively determined for this antibody; however, TPOAb has been used as a marker for autoimmune thyroid disease.[7,8]

Pulmonary hypertension is a progressive disease characterized by dyspnea, exercise limitation, and chest discomfort, often leading to right heart failure and death.[9,10] In an attempt to organize pulmonary hypertension, the World Health Organization (WHO) has classified pulmonary hypertension into five general groups.[11] An adaptation of the current WHO classification is shown in Table 1.[11] Pulmonary arterial hypertension (WHO Group 1) contains a number of subsets into which thyroid disorders have been included.[11] Indeed, thyroid disease has been associated with pulmonary hypertension for two decades.[12,13,14,15,16,17,18]

Current recommendations acknowledging an association between thyroid disease and pulmonary hypertension describe the need for further research, as it remains unclear whether or not thyroid disease is causally related to pulmonary arterial hypertension.[19] One prior publication advocated a systematic, comprehensive evaluation for thyroid disease in all patients with pulmonary arterial hypertension utilizing clinical, biochemical, and serologic parameters

Table 1. The Revised World Health Organization Classification of Pulmonary Hypertension*

Group 1. Pulmonary arterial hypertension
- Idiopathic
- Familial
- Related conditions: collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins, thyroid disorders, myeloproliferative disorders, splenectomy, hemoglobinopathies, glycogen storage disease
- Associated with significant venous or capillary involvement
- Persistent pulmonary hypertension of the newborn

Group II. Pulmonary venous hypertension
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Group III. Pulmonary hypertension associated with hypoxemia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group IV. Pulmonary hypertension due to chronic thrombotic disease, embolic disease, or both
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Pulmonary embolism

Group V. Miscellaneous
- Sarcoidosis, pulmonary Langerhan's-cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels

*The table has been adapted from Simonneau et al.[11]

of autoimmune thyroid disease.[20] Recognizing the correlation between autoimmune thyroid disease and pulmonary arterial hypertension, we postulated that screening for TPOAb would help to determine whether pulmonary arterial hypertension is associated with thyroid disease.

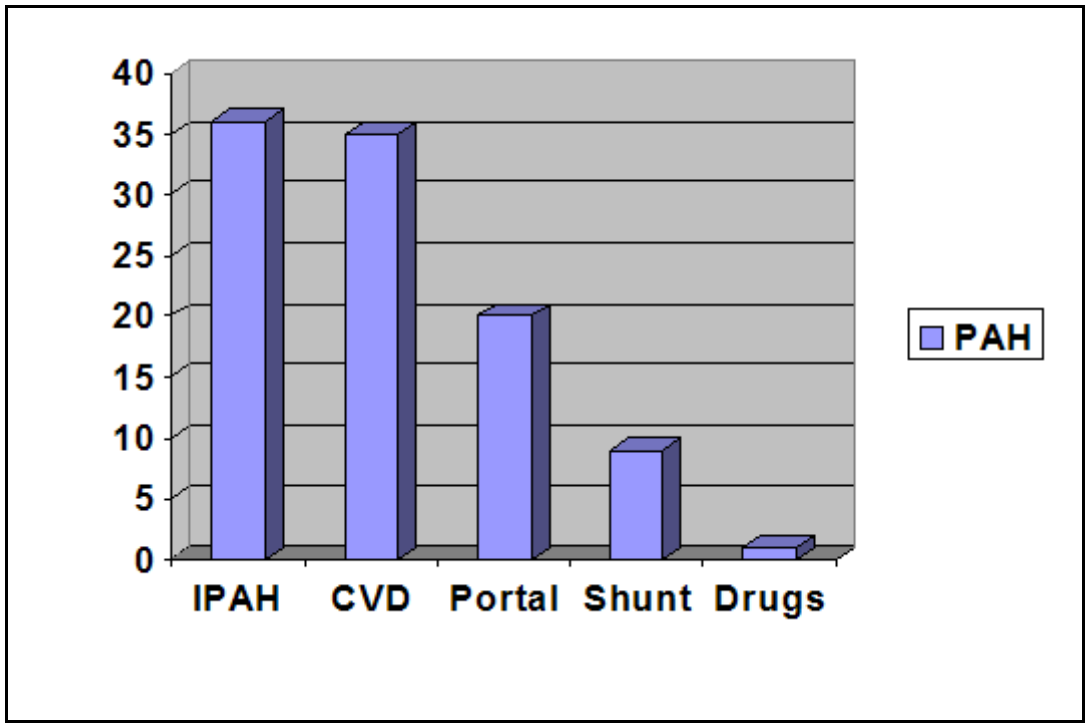
Materials and Methods

Patients. This study was approved by the Mayo Clinic Institutional Review Board. Consecutive patients with pulmonary arterial hypertension seen at Mayo Clinic Jacksonville Pulmonary Hypertension Center from 2001 to 2008 were studied retrospectively.

Data Collection. The following information was collected for the patients in this observational study: age, sex, pulmonary hypertension characteristics, and thyroid function test results. Pulmonary hypertension was defined as sustained mean pulmonary artery pressure >25 mm Hg at rest or systolic pulmonary arterial pressure >35 mm Hg. The diagnosis was confirmed by history, physical examination, echocardiography, right heart catheterization, and comorbid conditions.

Pulmonary venous hypertension was excluded by a pulmonary artery occlusion pressure ≤15 mm Hg. Information about the etiology of the patient's pulmonary arterial hypertension is shown in Figure 1. The mean pulmonary artery pressure in this cohort was 44 ± 14 mm Hg. Four patients were diagnosed with pulmonary arterial hypertension based on echocardiographic right ventricular systolic pressure >35 mmHg and had no reported mean pulmonary artery pressure.

Thyroid disease was determined by an abnormal thyroid function test result, or by a previous diagnosis of thyroid disease and the current use of thyroid replacement therapy. Hypothyroidism was defined by TSH levels >5.5 mIU/L (Hypersensitive Enzyme Immunoassay on Beckman Coulter DXI; reference range, 0.1 to 5.5 mIU/L); free thyroxine levels <0.8 ng/dL (immunoradiometric assay on Beckman Coul-



IPAH (Idiopathic Pulmonary Arterial Hypertension); CVD (Collagen vascular disease); Portal (Portal hypertension); Shunt (Congenital systemic-to-pulmonary shunts).

Coulter DXI; reference range, 0.8 to 1.4 ng/dL); or a history of thyroid disease treated with thyroid hormone replacement. Hyperthyroidism was defined by a TSH level < 0.1 mIU/L or a free thyroxine level > 1.4 ng/dL and no current use of thyroid hormone replacement. Autoimmune thyroid disease was defined as any of the aforementioned including an abnormal TPOAb level >20 IU/mL (reference value ≤ 20 IU/ml).

Statistical Analysis. Sensitivity, specificity, positive predictive value, and negative predictive value were determined for TPOAb measurements in the setting of thyroid disease as defined above utilizing the standard formulas.

Results

Of the 101 patients included in the study, 74 were female. Ages of the cohort ranged from 21 to 88 years, and the mean age was 62 years. Two patients were on continuous IV epoprostenol prior to evaluation. Thirty-seven of the study patients (37%) were found to have autoimmune thyroid disease.

Overall, 17 patients were positive for TPOAb, 15 patients were found to have an abnormal TSH levels, and 17 patients had a previous history of thyroid disease and were on thyroid hormone replacement. Of those with autoimmune thyroid disease, 32 were diagnosed with hypothyroidism, and 2 were diagnosed with hyperthyroidism. Two had abnormal TPOAb levels with normal TSH values and were not on thyroid hormone replacement.

The sensitivity of TPOAb testing in the setting of thyroid disease associated pulmonary arterial hypertension was 46% (CI 29 to 63%). The specificity was 97% (CI 89 to 99%), positive predictive value 89% (67 to 98%), and negative predictive value 76% (CI 65 to 84%). Of those with autoimmune thyroid disease, only 2 had elevated levels of TPOAb with a reference range TSH and an absence of thyroid hormone replacement.

Discussion/Conclusion

Our data indicate a incidence of thyroid disease in pulmonary hypertension (37%) similar to that reported in previous studies.[20,21,22] Other researchers have reported an incidence as high as 49%.[20] Due to the strong association of the two conditions, it may be reasonable to screen patients with pulmonary hypertension for the possibility of underlying autoimmune thyroid disease. It is not clear, however,

which test is most effective for screening.

The issue of how the screening should take place has been left open ended. This has resulted from the lack of a clear understanding of the association between pulmonary hypertension and autoimmune thyroid disease and the need for further evaluation of that association.

In recent studies, researchers have speculated on a common, underlying etiological link between the two conditions.[20,23,24] Possible associations include an as yet undiscovered immunogenetic overlap/ susceptibility, prostacyclin therapy, or an inflammatory process.[20,25,26]

TPOAb levels were abnormal in 17% of our population with autoimmune thyroid disease and pulmonary arterial hypertension. However, the elevated TPOAb levels added little-to-no value as compared to a TSH, a history of thyroid disease, and the current use of thyroid hormone replacement.

This low sensitivity of TPOAb demonstrates limited usefulness as a screening test for thyroid disease in pulmonary hypertension. In only two clinical cases were the TPOAb levels felt to be additive in this cohort of 101 patients. Neither of these cases involved underlying immunological disease or ongoing prostacyclin therapy; instead, they involved portal hypertension and end-stage liver disease due to Hepatitis C. In addition, both had failed treatment with alpha-interferon in the past prior to their evaluation. Incidences of autoimmunity developing after alpha-interferon as well as thyroid abnormalities in chronic viral hepatitis are well described in the literature and may account for this finding.[24,26,27]

Summary

This study reinforces the association between autoimmune thyroid disease and pulmonary arterial hypertension. However, we found testing for TPOAb to have low sensitivity. This makes it a poor screening test and an unlikely player in the future search for a common immunogenetic susceptibility.

While the majority of abnormal TPOAb levels were found in patients with thyroid disease, two cases represented patients having portal hypertension with end-stage liver disease secondary to hepatitis C; both patients had undergone alpha-interferon in the past. A TSH and history were adequate in evaluating the possibility of thyroid dysfunction in patients with pulmonary arterial hypertension.

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