High Prevalence of Autoimmune Thyroid Disease in Pulmonary Arterial Hypertension*

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Study objectives: An association between thyroid disease and pulmonary arterial hypertension (PAH) has been reported, yet the pathogenetic relationship between these conditions remains unclear. Because immune system dysfunction may underlie this association, we sought to determine the prevalence of autoimmune thyroid disease (AITD) in patients with PAH.

Design and setting: Prospective observational study at a single academic institution.

Patients: Sixty-three consecutive adults with PAH (ie, sustained pulmonary artery systolic pressure, > 25 mm Hg) were evaluated for clinical, biochemical, and serologic features of AITD.

Measurements: Thyroid gland dysfunction was determined by clinical examination for goiter, and by biochemical measurements of thyrotropin and free thyroxine. Immune system dysfunction was determined by serologic measurements of antibodies to thyroglobulin and thyroid peroxidase. First-degree family history of AITD also was ascertained in order to investigate for genetic clustering of autoimmunity.

Results: Thirty-one patients (49%; 95% confidence interval [CI], 37 to 62%) received diagnoses of AITD. Eighteen patients were newly diagnosed, and 9 patients required the initiation of pharmacologic treatment. There was no chronologic relationship between the diagnosis or treatment of PAH and that of AITD. Sixteen patients (25%; 95% CI, 15 to 36%) had 24 first-degree family members with AITD.

Conclusions: Approximately half of the patients with PAH have concomitant AITD. These two conditions may be linked by a common immunogenetic susceptibility, and the elucidation of this association may advance the understanding of the pathophysiology and treatment of PAH. Systematic surveillance for occult thyroid dysfunction in patients with PAH may prevent the hemodynamic exacerbation of right heart failure.

Key words: autoimmune thyroiditis; Graves disease; pulmonary hypertension; thyroid diseases

Primary pulmonary hypertension (PPH) is a rare progressive disorder of the pulmonary vasculature that causes early death from right heart failure. 1

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This disorder has commanded a great deal of attention as a result of its elusive pathophysiology, poor prognosis, and limited treatment options. The idiopathic form of PPH is extremely rare (incidence, one case per million population per year), but similar forms develop in association with collagen vascular disease, 2,3 liver disease, 4 HIV infection, 5 anorexigen usage, 6 and drug abuse. 7 The exposure-associated forms of pulmonary hypertension and idiopathic PPH are precipillary in nature, and they are clinically and histopathologically indistinguishable from each other. 1,2 All of these conditions have been classified as related forms of pulmonary arterial hypertension (PAH) by a World Health Organization consensus symposium, 5 but the common underlying disease mechanism remains obscure despite intensive research.
Prior retrospective studies have suggested an association between thyroid dysfunction and the diagnosis or treatment of PAH, and several case reports have described patients who received diagnoses of both pulmonary hypertension and thyroid disease. One study has reported a series of patients with PAH and hyperthyroidism, while four others have described a high retrospective prevalence (10 to 24%) of hypothyroidism or elevated levels of thyrotropin (TSH) in patients with PAH. In another retrospective study, a high frequency of thyroglobulin autoantibodies (30%) was noted in patients with PAH. Each of these studies, when considered separately, provides limited insight into the pathogenetic relationship between PAH and thyroid disease. None accurately determined the prevalence of thyroid disease in patients with PAH, as they were either retrospective or consisted solely of selected cases. All of the retrospective series also were characterized by incomplete evaluation of thyroid disease. Some determined the presence of thyroid disease only by chart review. Others assessed biochemical thyroid dysfunction (ie, levels of TSH and free thyroxine [FT4]) but did not test for the presence of thyroid autoantibodies and made no distinctions among autoimmune, drug-induced, surgical, or other causes of hypothyroidism or hyperthyroidism. The only study to evaluate for the presence of thyroglobulin antibodies (TgAbs) neither assessed thyroid function nor measured the more prevalent thyroid-peroxidase antibody (TPOAb). Furthermore, two retrospective reports speculated on a causal relationship between prostacyclin treatment of PAH and the diagnosis of thyroid disease, but both studies had observational biases and were inconclusive.

The forms of thyroid disease (hyperthyroidism, hypothyroidism, and TgAbs) that have each been described to occur in patients with PAH have thus far been considered distinct associations, without any unifying explanation. However, taking all of these reports together, one recognizes that Graves hyperthyroidism, Hashimoto hypothyroidism, and thyroid autoantibodies represent overlapping conditions in the autoimmune thyroid disease (AITD) syndrome, which is characterized by shared immune and genetic features. Thus, we hypothesized that the PAH-thyroid association is derived from a common immunogenetic susceptibility, and we initiated a prospective study of thyroid disease in patients with PAH to accomplish three major goals.

First, we sought to accurately determine the prevalence of AITD in patients with PAH by comprehensively evaluating the clinical, biochemical, and serologic parameters of thyroid disease. We hypothesized that there would be a high frequency of AITD and prominent familial clustering of AITD in patients with PAH. We also hypothesized that most detected forms of hypothyroidism and hyperthyroidism would be autoimmune in pathogenesis, rather than arising from medical or surgical treatment. Such findings would suggest a common genetic basis of PAH and AITD, with implications for novel diagnostic and therapeutic approaches to pulmonary hypertension. Second, we aimed to clarify the relationship between the diagnosis or treatment of PAH and that of AITD, since previous studies speculated that prostacyclin treatment might induce thyroid dysfunction, or, alternatively, that hypothyroidism might cause PAH. A prospective evaluation of AITD in patients with PAH would be able to elucidate the chronologic relationship between such events. Finally, we sought to identify and to promptly treat occult thyroid disease in all patients with PAH, because thyroid hormone imbalance can impact cardiac function, potentially perturbing the precarious hemodynamic state of patients with PAH.

Our study is the first prospective evaluation of thyroid disease in PAH patients and the only one to examine multiple features of AITD.

Materials and Methods

The Stanford University Human Subjects Committee approved this study, and each patient gave written informed consent before participating. We enrolled 63 consecutive adult patients (age, >18 years) who had received a diagnosis of PAH and had received continuing care at the Stanford Hospital Chest Clinic between August 1999 and December 2001. PAH was diagnosed by right heart catheterization findings of sustained mean pulmonary arterial pressures of >25 mm Hg at rest and was categorized according to the World Health Organization classification. Exclusion criteria consisted of secondary causes of pulmonary hypertension, including those related to left-sided myocardial or valvular disease, chronic hypoxia, chronic veno-occlusive disease, COPD or chronic restrictive pulmonary disease, or interstitial lung disease. These diagnoses were made by interview, examination, and clinical evaluation, which included the use of pulmonary function testing, pulmonary angiography, ventilation-perfusion scintigraphy, high-resolution CT scanning, polysomnography, and transesophageal echocardiography.

Each participant underwent a medical interview and thyroid examination, provided information about family history, and contributed blood samples for the evaluation of AITD. TSH levels (third generation immunometric assay; reference range, 0.40 to 4.00 μU/mL), FT4 levels (immunoradiometric assay; reference range, 0.73 to 2.01 ng/dL), and the presence and levels of TPOAbs and TgAbs (immunoradiometric assays; negative, <0.3 U/mL; abnormal level, >1.0 U/mL) were determined for each patient. The detection of thyroid dysfunction resulted in confirmatory testing before the initiation of pharmacologic treatment. All patients had repeat TSH and FT4 testing performed at follow-up, at intervals of 4 to 6 months.

Graves disease was defined by the finding of sustained hyperthyroidism (ie, low TSH levels and high FT4 levels), a diffuse goiter, and elevated homogenous uptake on 123I scintigraphy. Hashimoto disease was defined by the presence of at least two of the following three criteria: (1) thyroid autoantibodies; (2) re-
peatedly elevated TSH levels; and (3) diffuse goiter. The presence of thyroid autoantibodies or either of the above conditions defined AITD. None of the patients had been exposed to amiodarone, interferon-α, or lithium within the past year, or to iodinated contrast material within 2 months before the initial thyroid function testing.

Descriptive statistics include percentages for categoric variables and means ± SD for continuous measures. The χ² test with the Yates correction factor was used to make statistical comparisons.

Results

The mean age of the cohort was 47 years (range, 19 to 79 years), there were 53 women and 10 men, and PAH had been diagnosed for a mean duration of 2.7 years (range, 0.1 to 11.5 years). At the time of the initial thyroid function evaluation, 15 patients were receiving continuous IV epoprostenol (Flolan; GlaxoSmithKline; Research Triangle Park, NC) by infusion therapy, 2 patients were taking subcutaneous uniprost (Remodulin; United Therapeutics; Silver Spring, MD), and 1 patient was a heart-lung transplant recipient. The mean follow-up period was 1.0 years (range, 0.1 to 2.3 years). At the most recent evaluation, 8 patients were deceased, 30 patients were receiving therapy with epoprostenol, 2 patients were receiving therapy with uniprost, 3 patients were receiving therapy with oral bosentan (Tracleer; Actelion Ltd; Basel, Switzerland), and 1 patient had received a transplant. Thirty-one of the study patients (49%; 95% confidence interval, 37 to 62%) were found to have AITD. Sixteen individuals (8 with AITD) had a total of 24 first-degree family members who were receiving treatment either for Graves disease or Hashimoto disease.

AITD affected patients across all subgroups of PAH (Table 1). The highest prevalence was seen in the group with idiopathic PPH (67%). Overall, 21 patients were positive for TPOAb, 18 patients were positive for TgAb, 13 patients were positive for both, and 5 patients were negative for both. Thirteen individuals carried prior diagnoses of AITD, while 18 patients were newly diagnosed, with 9 requiring the initiation of pharmacologic intervention (4 for Graves disease and 5 for Hashimoto disease). All of the patients with thyroid dysfunction requiring pharmacologic treatment had autoimmune causes of hypothyroidism (ie, Hashimoto disease and lymphocytic hypophysitis) or hyperthyroidism (Graves disease) [Table 2].

Thirty-five of the 63 patients had recently (ie, < 3 months ago) received a diagnosis of PAH. The longitudinal thyroid test results in this subgroup provide a valid prospective evaluation of the temporal relationships between the diagnosis or treatment of thyroid disease and that of PAH. Seventeen of these 35 patients were found to have AITD. Four carried prior diagnoses of AITD, 12 received diagnoses of AITD at the initial visit to our institution, while 1 patient was initially euthyroid with negative test results for the presence of thyroid autoantibodies and developed Graves disease 9 months after the initiation of epoprostenol therapy. Of the 12 individuals with occult AITD, 4 were hypothyroid, 4 were hyperthyroid, and 4 were euthyroid with high-titer thyroid autoantibodies and goiter.

How does the prevalence of AITD in PAH patients compare with that of the general population? The percentage of PAH-afflicted patients necessitating medical therapy for AITD (33%) was dramatically higher than the 15% of patients with thyroid dysfunction in the Colorado cohort (p < 0.0001). The frequency of treated AITD in the subgroup of women (38%) was considerably higher than the 13% of women requiring treatment for AITD that was noted in the 20-year longitudinal Whickham survey (p < 0.0001), despite a younger age distribution in the women with PAH (mean, 46 vs 55 years, respectively). The frequency of the presence of first-degree family history of AITD (25%) was also significantly higher in the PAH cohort when compared to the general population findings (5.5%; p < 0.001).

Table 1—Frequency of AITD Characteristics in Patients With PAH

<table>
<thead>
<tr>
<th>Type of PAH</th>
<th>No.</th>
<th>Age, mean yr</th>
<th>Female</th>
<th>White</th>
<th>TPOAb (+)</th>
<th>TgAb (+)</th>
<th>AITD</th>
<th>Rx AITD</th>
<th>FHx AITD</th>
<th>AITD Rx AITD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PPH</td>
<td>24</td>
<td>48</td>
<td>20 (83)</td>
<td>16 (67)</td>
<td>12 (50)</td>
<td>11 (46)</td>
<td>16 (67)</td>
<td>10 (42)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>CTD-associated</td>
<td>13</td>
<td>49</td>
<td>13 (100)</td>
<td>9 (69)</td>
<td>1 (8)</td>
<td>2 (15)</td>
<td>5 (38)</td>
<td>3 (23)</td>
<td>5 (38)</td>
<td></td>
</tr>
<tr>
<td>Liver disease-associated</td>
<td>6</td>
<td>46</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td>Drug abuse-associated</td>
<td>11</td>
<td>41</td>
<td>6 (73)</td>
<td>10 (91)</td>
<td>3 (27)</td>
<td>1 (9)</td>
<td>4 (36)</td>
<td>3 (27)</td>
<td>3 (27)</td>
<td></td>
</tr>
<tr>
<td>Anorexigen-associated</td>
<td>6</td>
<td>52</td>
<td>6 (100)</td>
<td>6 (100)</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>4 (67)</td>
<td>3 (50)</td>
<td>2 (33)</td>
<td></td>
</tr>
<tr>
<td>HIV infection-associated</td>
<td>3</td>
<td>30</td>
<td>2 (67)</td>
<td>2 (67)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Entire cohort</td>
<td>63</td>
<td>47</td>
<td>53 (84)</td>
<td>48 (76)</td>
<td>21 (33)</td>
<td>18 (29)</td>
<td>31 (49)</td>
<td>21 (33)</td>
<td>16 (25)</td>
<td></td>
</tr>
</tbody>
</table>

Values given as No. (%), unless otherwise indicated. CTD = connective tissue disease (including systemic lupus erythematosus, scleroderma, rheumatoid arthritis, etc); FHx AITD = has first-degree family history of AITD; Rx AITD = requiring pharmacologic treatment for AITD.

*Seven patients were receiving immunomodulatory agents, which may suppress thyroid autoantibody formation.

†Either amphetamine and/or cocaine abuse.
PAH results from complex, poorly understood interactions between genetic factors and environmental triggers. Genetic studies identified bone morphogenetic protein receptor-II mutations in patients manifesting familial and sporadic PPH. Additional genetic factors potentiating immune dysfunction also may be involved, since the following features of autoimmune disease are commonly observed in PAH patients: marked female gender predominance; distinctive human leukocyte antigen haplotypes; high frequency of autoantibodies; concomitant connective tissue disease; and disease reversal with immunosuppressive therapy. The results of this study support the presence of immune dysfunction in PAH-affected individuals, since 49% had evidence of AITD. The high frequency of PAH patients with first-degree family histories of AITD, even in those without a personal history of AITD, further suggests the presence of immunogenetic clustering.

The 49% prevalence of AITD in PAH patients is striking, exceeding the frequency found in any of several well-characterized autoimmune diseases that are associated with AITD. These include type 1 diabetes mellitus, Addison disease, and pernicious anemia, which aggregate in the polyglandular autoimmune syndromes. Also associated with AITD are nonendocrine disorders including myasthenia gravis and the collagen vascular diseases. Of these various conditions, connective tissue diseases have been described previously to associate separately with either AITD or PAH and collagen vascular disorders. The potential immunogenetic overlap between PAH and AITD is further supported by data on the use of interferon-α, which has been shown to induce autoimmune disorders, and is also associated with the development of PAH. With multiple lines of evidence suggesting immune dysfunction in PAH patients, the role of immunoregulatory agents in treating early PAH should be examined. Currently, only incidental data exist on the efficacy of immunosuppressive agents to attenuate elevated pulmonary artery pressures in patients with pre-existent autoimmune connective tissue disorders.

This report is the first prospective and systematic evaluation of thyroid dysfunction in PAH patients with the use of clinical, biochemical, and serologic parameters of AITD. The collective AITD prevalence of 49% is the highest reported frequency of thyroid dysfunction in PAH patients, yet the prevalence of individual measurements of thyroid disease resembles those of previous observations, supporting the general applicability of these findings. For example, our presurvey prevalence of hypothyroidism (19%) was within the range of retrospectively determined rates of 10 to 24%. The TgAb prevalence (29%) in this cohort is virtually identical to the previously reported 30% rate. Despite the high overall prevalence of AITD, it may yet be an underestimation, because six patients without thyroid disease were treated with immunosuppressants, which can mitigate the development of AITD.

On the basis of retrospective analyses, previous authors have speculated that prostacyclin treatment of PAH patients may lead to thyroid disease or, alternatively, that thyroid dysfunction may lead to PAH. However, the results from this study demonstrate a lack of chronologic relationship between the diagnosis or treatment of AITD and either PAH diagnosis or prostacyclin therapy initiation. Of the 35 patients in this cohort who were newly diagnosed with PAH, and thus could be validly assessed for thyroid dysfunction on a prospective basis, 17 patients were confirmed to have AITD, but only 1 of

Table 2—Frequency of Specific Diagnoses of Thyroid Disease in 31 Patients With Concurrent PAH and AITD

<table>
<thead>
<tr>
<th>Type of PAH</th>
<th>Hashimoto Disease</th>
<th>Graves Disease</th>
<th>Euthyroid With Thyroid Antibodies</th>
<th>Others</th>
<th>Total AITD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PPH</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>CTD-associated</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Liver disease-associated</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Drug abuse-associated†</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Anorexigen-associated‡</td>
<td>2</td>
<td>1</td>
<td>1§</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HIV infection-associated</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>31</td>
</tr>
</tbody>
</table>

*See Table 1 for abbreviations not used in the text.
†Patient had received putative diagnosis of lymphocytic hypophysitis and was hypothyroid.
‡Either amphetamine and/or cocaine abuse.
§Patient had received diagnosis of lymphocytic hypophysitis.
these patients developed thyroid disease after the initiation of prostacyclin therapy. Of the 12 patients with newly diagnosed PAH who were also newly found to haveAITD, 4 were hypothyroid, 4 were hyperthyroid, and 4 were euthyroid with thyroid autoantibodies. This suggests that the pathogenesis of PAH does not derive from the particular direction of disturbance in thyroid hormone concentrations. However, it is possible that abnormal circulating levels of thyroid hormone may have exacerbated right heart dysfunction, leading to an earlier diagnosis of PAH in several patients.

A substantial 29% of the entire cohort of patients were newly diagnosed withAITD, and half of these patients had abnormal results of thyroid function tests, requiring the initiation of pharmacologic treatment. These findings strongly advocate for a systematic, comprehensive evaluation of thyroid disease in all patients with PAH, including the assessment of both serologic and biochemical parameters. Thyroid autoantibodies are important, because high titers in the euthyroid individual indicate incipientAITD, which may portend future thyroid dysfunction, and should prompt frequent thyroid function monitoring in the patient with PAH. Biochemical tests for TSH, FT4, and free triiodothyronine concentrations are critical for discovering occult thyroid disease, since objective findings of dysthyroidism are often nonspecific and subtle, and may be masked by severe symptoms that are associated with pulmonary hypertension. The most commonly detected thyroid function abnormality, subclinical hypothyroidism (ie, elevated TSH levels and normal FT4 levels) may not often need to be treated in the healthy ambulatory individual, but in the patient with PAH with a tenuous cardiac reserve, appropriate thyroid hormone treatment may improve hemodynamic function. In our cohort, symptomatic improvement was reported by the nine patients with newly diagnosed hypothyroidism or hyperthyroidism after the treatment of thyroid disease, but the concomitant initiation or modification of PAH therapy during the time interval (ie, > 1.5 months) required for the achievement of euthyroidism confounded these observations. However, one would generally expect improved circulatory and respiratory function with the restoration of normal thyroid function.

In summary, this study has demonstrated a dramatic association betweenAITD and PAH, with evidence for a common immunogenetic susceptibility. The approach of identifying in PAH-affected patients the collective syndrome ofAITD, rather than its separate components, provides a unifying explanation for previously observed associations among PAH and hypothyroidism, hyperthyroidism, or the presence of thyroid autoantibodies. Future studies should focus on discovering the immunogenetic overlap betweenAITD and PAH, such as common human leukocyte antigen alleles, susceptibility loci, autoantibodies and/or autoantigens, and the mechanisms of immune dysfunction. Such an improved understanding of the genetic and immune factors causing PAH may ultimately lead to novel effective approaches in diagnosis and treatment.