ASK THE EXPERT

What Is the Association Between Thyroid Disease and Pulmonary Hypertension: Do Pulmonary Arterial Hypertension Patients Need a Closer Look?

Section Editor
Sean M. Studer, MD, MSc, FCCP

Christopher S. King, MD, FACP, FCCP
Director, Advanced Lung Disease and Transplant Critical Care Services
Inova Fairfax Hospital
Falls Church, VA

Oksana A. Shlobin, MD, FCCP
Director, Pulmonary Hypertension Program
Advanced Lung Disease and Transplant Clinic
Inova Fairfax Hospital
Falls Church, VA

Thyroid hormone exerts numerous effects on the cardiovascular system through a number of mechanisms including direct effects on the heart and via interactions with the autonomic nervous system, vascular bed, and endothelium.[1] A wealth of observational data supports a link between pulmonary hypertension (PH) and thyroid disease.[2-5] In the largest reported series, Li and colleagues found a prevalence of thyroid disease to be 24% in PH patients (n=356) as compared to 15% in age- and sex-matched controls (n=698).[3] This finding was further validated by the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), which reported comorbid thyroid disease in 21.6% of 2525 PH patients.[6] Across these studies, hypothyroidism was the predominant thyroid abnormality and prevalence was highest in patients with World Health Organization (WHO) Group 1 pulmonary hypertension (pulmonary arterial hypertension [PAH]). Hyperthyroidism has also been associated with PH. Numerous case reports describe new-onset PH, often severe, in the setting of Graves' disease or multinodular goiter-induced hyperthyroidism.[7] In the majority of these cases PH improves or resolves with treatment of hyperthyroidism. Initiation of prostanoid therapy has also been reported to precede development of thyrotoxicosis and goiter formation, possibly due to direct effects of the medication on thyroid tissue.[8]

The exact mechanisms for the relationship between thyroid disease and PH remain poorly understood. Badesch and colleagues hypothesized that autoimmunity may play a causative role in the development of both conditions.[9] This conjecture is supported by a high incidence of autoimmune thyroid disease in idiopathic PAH. In fact, Chu et al diagnosed autoimmune thyroid disease in half of patients with PAH in a small prospective observational study.[4] Other postulated mechanisms include the direct effects of thyroid hormone on the cardiovascular and endothelial systems. In hyperthyroidism, cardiac output is raised through increases in both heart rate and contractility. Thyroid hormone also decreases peripheral vascular resistance and mean arterial pressure through direct effects on vascular smooth muscle, leading to activation of the renin-angiotensin-aldosterone system and increased sodium absorption and blood volume. Hyperthyroidism also can reduce production of pulmonary vasodilators including nitric oxide and prostacyclin, and increase pulmonary vasoconstrictors including endothelin-1.[7] In hypothyroidism, low thyroid hormone levels result in increased systemic vascular resistance and decreased cardiac contractility, leading to increased pulmonary venous pressures.[1] Hypothyroidism also causes vascular inflammation, which may promote angioproliferation in the pulmonary vasculature leading to development of PAH.[1]

While the prevalence and mechanisms for a link between thyroid disease and PH are interesting, what clinicians really care about is how it affects their patients. The best data to date come from a retrospective analysis of 1756 patients by Richter and colleagues.[10] They found that in patients with idiopathic PAH, both abnormally high and low thyroid-stimulating hormone (TSH) levels were associated with an increased risk for death. Similarly, in patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH), low free T3 levels were associated with increased mortality.[10] These results, while intriguing, should be interpreted with caution as retrospective study design precludes any firm conclusion regarding a causal relationship between thyroid function testing (TFT) or treatment of thyroid disease and outcomes.

As one can see from the above data, we still have much to learn about the association between thyroid disease and PH. Given what we do know, how should clinicians approach evaluation and treatment of thyroid disease in this patient population? To our knowledge, there are no guidelines regarding a recommended approach to screening and treatment of thyroid disease in PH. At our center, we obtain TFTs at the initial evaluation of all patients being evaluated for PH. Patients with normal TFTs and no history of thyroid disease continue to get yearly screening with TSH. Additionally, TFTs are obtained if any clinical signs or symptoms of either hypothyroidism (cold intolerance, weight gain, marked fatigue) or hyperthyroidism (tachycardia, heat intolerance, tremor, arrhythmias) develop. Given

the possible causal relationship between prostanoids and hyperthyroidism, we also repeat TFTs 3 months after initiation of therapy. In patients with known thyroid disease on replacement therapy, TFTs are checked every 6 months.

Treatment of thyroid disease does not differ from the approach in patients without PH. In the case of hypothyroidism, thyroid replacement therapy is initiated in consultation with endocrinology colleagues. As with other cardiac conditions, conservative dosing up front with gradual uptitration is prudent to avoid iatrogenic hyperthyroidism. The decision to treat subclinical hypothyroidism, defined as a normal free T4 but an elevated TSH, remains a matter of debate. Given the association of elevated TSH with increased mortality in PH patients, closely monitored treatment should be considered, especially in symptomatic patients. We employ an aggressive approach to treatment of hyperthyroidism with standard treatments including radioactive iodine and/or antithyroid medication.

In summary, epidemiologic data point to a link between PH and thyroid disorders. Numerous mechanisms make this relationship biologically plausible. The limited data available suggest that abnormal thyroid function may be associated with adverse outcomes in PH patients. Based on currently available information, we suggest that PH centers develop a standardized approach to screening for thyroid disease in PH patients. Particular vigilance is warranted in patients on prostanoid therapy, as this class of drugs has direct effects on the thyroid gland.

References

1. Scicchitano P, Dentamaro I, Tunzi F, et al. Pulmonary hypertension in thyroid diseases. *Endocrine*. 2016;54(3):578-587.
2. Curnock AL, Dweik RA, Higgins BH, Saadi HF, Arroliga AC. High prevalence of hypothyroidism in patients with primary pulmonary hypertension. *Am J Med Sci*. 1999;318(5):289-292.
3. Li JH, Safford RE, Aduen JF, Heckman MG, Crook JE, Burger CD. Pulmonary hypertension and thyroid disease. *Chest*. 2007;132(3):793-797.
4. Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. *Chest*. 2002;122(5):1668-1673.
5. Ferris A, Jacobs T, Widlitz A, Barst RJ, Morse JH. Pulmonary arterial hypertension and thyroid disease. *Chest*. 2001;119(6):1980-1981.
6. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest*. 2010;137(2):376-387.
7. Vallabhajosula S, Radhi S, Cevik C, Alalawi R, Raj R, Nugent K. Hyperthyroidism and pulmonary hypertension: an important association. *Am J Med Sci*. 2011;342(6):507-512.
8. Chadha C, Pritzker M, Mariash CN. Effect of epoprostenol on the thyroid gland: enlargement and secretion of thyroid hormone. *Endocr Pract*. 2009;15(2):116-121.
9. Badesch DB, Wynne KM, Bonvallet S, Voelkel NF, Ridgway C, Groves BM. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? *Ann Intern Med*. 1993;119(1):44-46.
10. Richter MJ, Sommer N, Schermuly R, et al. The prognostic impact of thyroid function in pulmonary hypertension. *J Heart Lung Transplant*. 2016;35(12):1427-1434.