A Case of CTEPH: Reviewing the Literature to Explain Paradoxical Link to Hypothyroidism

William Ciurylo, DO PGY-1, Peter Saikeli, MD
HCA/Tufts Portsmouth Regional Hospital, Portsmouth, NH

Background

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a World Health Organization group IV variant of pulmonary hypertension. It is associated with significant morbidity and mortality.

Both hypothyroidism and thyroid replacement have been considered risk factors for the development of CTEPH.

Residual organized clot is thought to remain at the end vessel with subsequent fibrosis and vascular remodeling impeding blood flow.

But, it has been demonstrated that hyperthyroidism confers hypercoagulability, while hypothyroidism is thought to be anticoagulant with associated reduction in clot resolution times.

It is therefore, unclear how a condition otherwise associated with hypercoagulability is associated with hypothyroidism.

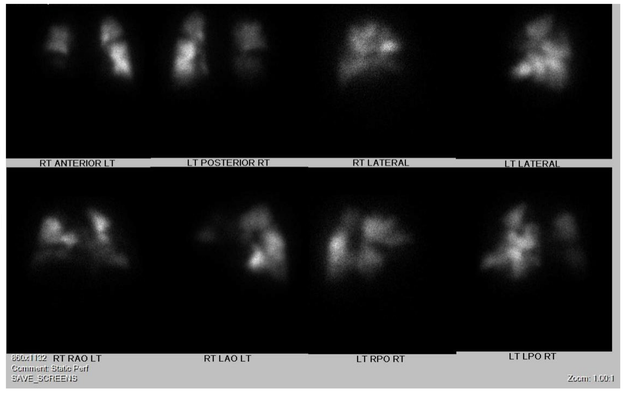
Objective

- To explore the literature on this topic to find a possible underlying mechanism to explain this paradoxical relationship
- To provide an example of CTEPH encountered in a clinical setting
- To establish foci for future research into the pathophysiology, treatment, and prevention of CTEPH

The Case

A 58 year old male was admitted with complaint of acute on chronic dyspnea. Patient history is remarkable for two unprovoked deep vein thrombosis with indefinite Rivaroxaban treatment, extensive work-up for possible seronegative rheumatoid arthritis versus polymyalgia rheumatica with concomitant gout on prednisone and hydroxychloroquine, Hashimoto's Thyroiditis for which he takes Synthroid, and a recent unremarkable stress echocardiogram for shortness of breath. Social hx notable for medication noncompliance. He endorses a sudden onset dyspnea four months ago, lasting one week, with intervening honeymoon period of resolution, before recurrence of dyspnea five days ago, with progression. Patient with new nasal canula requirement. Arterial Blood Gas with pH 7.45, pCO2 31, pO2 82, and HCO3 21.0. Labs notable for Troponin I peak of .166, ProBNP 6160 pg/mL, C-Reactive Protein 40.9. TSH Markedly elevated to 75.90. Diagnostics as below:

V/Q Scan demonstrating heterogeneous radiotracer distribution with multiple moderate to large peripheral subsegmental perfusion defects within each lung



Hypothyroidism and CTEPH

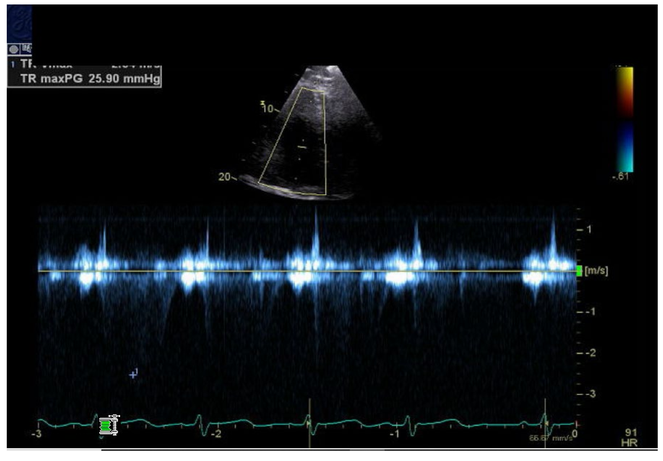
- Krieg et al (2019) found that 24.1% of patients with operable CTEPH had a history of thyroid dysfunction of any kind
  - Patients with hypothyroid function, with Hashimoto's thyroiditis being the most common variant, had more severe CTEPH
- In a study of 772 patients diagnosed with acute pulmonary embolism, Those with hypothyroidism were more likely to be diagnosed with CTEPH during follow-up
- Richter et al. in 2016 concluded that thyroid hormone levels and THR therapy are prognostic factors in iPAH, PAH, and CTEPH
- No risk association has been found between anti-TPO levels and thrombotic risk.

Thyroid Hormone and Clot Non-Resolution

Hyperthyroidism is Pro-Coagulant	
Associated changes include: • Increased von Willebrand Factor • Increased fibrinogen • Increased Fibronectin • Increased Thrombomodulin • Increased PAI-1 • Increased Clotting Factors • Increased thrombin-activatable fibrinolysis inhibitor	 • Decreased Plasminogen • Decreased t-PA • Decreased platelet adhesion time • Decreased platelet aggregation time • Decreased clot lysis

Hypothyroidism is Anti-Coagulant	
Associated changes include: • Increased Bleeding Time • Increased PT, aPTT • Increased von Willebrand Factor • Increased Thrombomodulin • Hyperfibrinolysis	 • Decreased Clotting Factors • Decreased t-PA • Decreased platelet adhesion time • Decreased platelet aggregation time • Decreased clot lysis

Tricuspid regurgitation peak velocity of 2.5 m/sec with tricuspid peak RV-RA gradient of 26 mmHg allowing for assessment of pulmonary hypertension with estimated pulmonary arterial pressures of 34 mmHg



Thyroid Hormone, Angiogenesis, Neovascularization, and Vascular Remodeling

Angiogenesis and Neovascularization are crucial to clot resolution, vascular remodeling occurs as the artery responds to changes in shear stress and oxygenation after an obstructing thrombus

- Thyroid hormone has been demonstrated favorable to angiogenesis like Fibroblast growth factor, VEGF, and Angiopoietin-2
- Thyroid hormones have also been shown to stimulate neovascularization via bradykinin and angiotensin II pathways
- Angiogenesis and neovascularization is crucial to recanalization in pulmonary embolism
- Thyroid hormone has been shown to act directly on vascular smooth muscle as a vasodilator.

Patients with hypothyroidism impair vascular smooth muscle relaxation by reduced availability of nitrous oxide

Arterial atherosclerosis is enhanced by hypothyroidism, further impairing vascular functionality

Hypothyroidism may be permissive of inflammation and fibrosis leading to a fixed stenosis

Discussion

Our patient presented with positive V/Q scan, gold standard for CTEPH imaging, and pulmonary hypertension on echocardiography. His acute onset dyspnea followed by a honeymoon period and then a progressive dyspnea has been suggested to be characteristic of CTEPH. He was discharged with plan for surveillance. Pulmonary artery endarterectomy may be indicated for him in the future. CTEPH developing in this patient may have been assisted by his hypothyroidism. Hypothyroidism seems to alter the ability of his pulmonary arteries to make homeostatic changes in response to a pulmonary embolism. We suspect our patient had an undiagnosed acute pulmonary embolism, with Rivaroxaban noncompliance, four months prior to presentation. Hyperthyroidism may confer a risk for pulmonary embolism but hypothyroidism may make it challenging for the pulmonary vasculature to respond to it.

Conclusion

- On Review of the literature on this topic, the risk of CTEPH in patients with hypothyroidism is conferred by the vascular changes that occur in the absence of thyroid hormone
- Vessel recanalization may be limited, pulmonary arteries may be limited in their ability to respond to changes in sheer stress/hypoxia, and a permissive inflammatory environment may promote fibrosis, fixing stenosis of the pulmonary vasculature
- More research is needed into the pathophysiology of CTEPH
- Prevention of CTEPH may come from interventions that support arterial dilatation and vascular remodeling post-pulmonary embolism

References

1. The pathophysiology of chronic thromboembolic pulmonary hypertension. Gérald Simonneau, Adam Torbicki, Peter Dorfmüller, Nick Kim. European Respiratory Review Mar 2017, 26 (143) 160112; DOI: 10.1183/16000617.0112-2016
2. Tudoran C, Tudoran M, Vlad M, Balas M, Pop GN, Parv F. Echocardiographic evolution of pulmonary hypertension in female patients with hyperthyroidism. Anatol J Cardiol. 2018;20(3):174-181. doi:10.14744/AnatolJCardiol.2018.37096
3. Krieg VJ, Hobohm L, Liebetrau C, Guth S, Kölmel S, Troidl C, Mayer E, Konstantinides SV, Wiedenroth CB, Lankeit M. Risk factors for chronic thromboembolic pulmonary hypertension - Importance of thyroid disease and function. Thromb Res. 2020 Jan;185:20-26. doi: 10.1016/j.thromres.2019.10.025. Epub 2019 Oct 31. PMID: 31734602.
4. Richter MJ, Sommer N, Schermuly R, Grimminger B, Seeger W, Tello K, Ghofrani HA, Gall H. The prognostic impact of thyroid function in pulmonary hypertension. J Heart Lung Transplant. 2016 Dec;35(12):1427-1434. doi: 10.1016/j.healun.2016.05.022. Epub 2016 Jun 3. PMID: 27373820.
5. Elbers, LPB, Fliers, E, Cannegieter, SC. The influence of thyroid function on the coagulation system and its clinical consequences. J Thromb Haemost 2018; 16: 634– 45.
6. STUIJVER, D.J.F., HOOPER, J.M.W., ORME, S.M., Van ZAANE, B., SQUIZZATO, A., PIANTANIDA, E., HESS, K., ALZAHRANI, S. and AJJAN, R.A. (2012), Fibrin clot structure and fibrinolysis in hypothyroid individuals: the effects of normalising thyroid hormone levels. Journal of Thrombosis and Haemostasis, 10: 1708-1710. https://doi.org/10.1111/j.1538-7836.2012.04789.x
7. Bochenek ML, Leidinger C, Rosinus NS, Gogiraju R, Guth S, Hobohm L, Jurk K, Mayer E, Münzel T, Lankeit M, Bosmann M, Konstantinides S, Schäfer K. Activated Endothelial TGFβ1 Signaling Promotes Venous Thrombus Nonresolution in Mice Via Endothelin-1: Potential Role for Chronic Thromboembolic Pulmonary Hypertension. Circ Res. 2020 Jan 17;126(2):162-181. doi: 10.1161/CIRCRESAHA.119.315259. Epub 2019 Nov 21. PMID: 31747868; PMCID: PMC7101077.
8. Cohen K, Flint N, Shalev S, Erez D, Baharal T, Davis PJ, Hercbergs A, Ellis M, Ashur-Fabian O. Thyroid hormone regulates adhesion, migration and matrix metalloproteinase 9 activity via αvβ3 integrin in myeloma cells. Oncotarget. 2014 Aug 15;5(15):6312-22. doi: 10.18632/oncotarget.2205. PMID: 25071016; PMCID: PMC4171632.
9. Davis PJ, Davis FB, Mousa SA. Thyroid hormone-induced angiogenesis. Curr Cardiol Rev. 2009 Jan;5(1):12-6. doi: 10.2174/157340309787048158. PMID: 20066142; PMCID: PMC2803282.
10. Aysar Al Husseini, Gianluca Bagnato, Laszlo Farkas, Jose Gomez-Arroyo, Daniela Farkas, Shiro Mizuno, Donatas Kraskauskas, Antonio Abbate, Benjamin Van Tassel, Norbert F. Voelkel, Harm Jan Bogaard
11. European Respiratory Journal Jan 2013, 41 (1) 104-114; DOI: 10.1183/09031936.00196511
12. Toyoda N, Yasuzawa-Amano S, Nomura E, et al. Thyroid hormone activation in vascular smooth muscle cells is negatively regulated by glucocorticoid. Thyroid. 2009;19(7):755-763. doi:10.1089/thy.2009.0044
13. Mancini A, Di Segni C, Raimondo S, et al. Thyroid Hormones, Oxidative Stress, and Inflammation. Mediators Inflamm. 2016;2016:6757154. doi:10.1155/2016/6757154

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.