

Severe pulmonary hypertension: The role of metabolic and endocrine disorders

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a multi-factorial condition and the underlying pulmonary vascular disease is shaped by the combined action of genetic, epigenetic and immune-related factors. Whether and how gender, obesity and the metabolic syndrome modify PAH and associated right heart failure is under intense investigation. Estrogens may enhance the process of pulmonary angioproliferation, but may also protect the right ventricle under pressure. Obesity may affect the pulmonary circulation via interactions with inflammatory cells and mediators, or via alterations in endocrine signaling. Obesity is a major risk factor for pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved LV ejection fraction. Given the overlap between PAH and autoimmune diseases, hypothyroidism in patients with PAH is commonly considered a consequence of an autoimmune thyroiditis. In the clinical setting of hyperthyroidism, severe pulmonary hypertension may develop due to a hyperdynamic circulation, but a more complex situation presents itself when hyperthyroidism is associated with PAH. We recently showed in a relevant animal model of severe PAH that thyroid hormone, via its endothelial cell-proliferative action, can be permissive and drive angioproliferation. Signaling via the integrin $\alpha v \beta 3$ and FGF receptors may participate in the formation of the lung vascular lesions in this model of PAH. Whether thyroid hormones in euthyroid PAH patients play a pathobiologically important role is unknown- as we also do not know whether the commonly diagnosed hypothyroidism in patients with severe PAH is cardioprotective. This brief review highlights some recent insights into the role of metabolic and endocrine disorders in PAH.

Key Words: pulmonary hypertension, right heart failure, epigenetics, thyroid, obesity, gender

Pulmonary hypertension (PH) has been clinically classified or categorized, and mechanistically the four descriptors introduced by Paul Wood: vasoconstrictive, vasoobstructive, hyperkinetic, and passive (left heart failure) continue to be useful.^[1] Although the clinical classification distinguishes between pulmonary arterial hypertension (PAH; Group 1), pulmonary venous hypertension (Group 2), and pulmonary hypertension associated with thrombotic or embolic disease (Group 4), PAH (Group 1) combines at least three of the pathogenetically important mechanisms: vasoconstriction, hyperkinesis and vasoobliteration. Hyperkinesis plays an etiological role in PAH associated with congenital cardiac shunt abnormalities, porto-pulmonary hypertension, hyperthyroid disease-associated PAH and PAH associated with sickle cell anemia are all hyperkinetic, high cardiac

output forms of severe PAH.^[2-4] Clearly PAH, as classified, is a group of diseases with different long-term survival likely requiring different treatments.^[5] Not only is PAH not a single disease, but it is also increasingly appreciated that disease-specific pathobiologically important mechanisms and neuroendocrine factors shape the disease and determine outcome in individual patients. For example, autoimmunity/inflammation plays an important role in patients with systemic lupus erythematosus-associated pulmonary hypertension and in HIV/AIDS-associated PAH.^[6,7] Both genetic susceptibility factors and epigenetic influences need to be investigated for a more complete understanding of the pathobiology of PAH.^[8] Thyroid disease and obesity are likely epigenetic disease modifiers, and if the REVEAL registry data

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are representative; then pulmonary hypertension has now become overwhelmingly a disease of menopausal women.^[8-11] A large number of publications have confirmed the initial report of an association of hypothyroidism and PAH and a recent review by Biondi et al established a strong link between Graves disease and multinodular goiter and PAH.^[2,12-16] According to Biondi et al., more than 80% of patients with hyperthyroid diseases develop pulmonary hypertension. In this review, we wish to put PAH in a wider neuroendocrine disease context and summarize recent experiments which had been designed to investigate a functional role of thyroid hormones in the development of PAH.

ENDOCRINE MODIFIERS OF PULMONARY HYPERTENSION

The association between PAH and hypothyroid disease hypothetically suggests that the patients had at some time experienced an autoimmune thyroiditis, and this association is cited as evidence of a participation of the immune system in the pathogenesis of PAH.^[17] However, the broader context may be estrogen and other hormone-dependent mechanisms of disease development or disease modification (Fig. 1). In addition to endocrine factors which may modify the pathogenesis there are neuroendocrine factors which enter the stage as right heart failure develops; these are hyperaldosteronism and sympathetic overdrive.^[19]

Obesity, which is now understood as an inflammatory disease, may be a cotrigger of PAH or may worsen the

inflammatory contribution of chronic pulmonary vascular diseases.^[20,21] Sweeney et al. in a survey of 88 patients with PAH found that 25% had a body mass index (BMI) of 30 kg/m² or greater.^[9] Epidemiological data suggest a significant association between increasing BMI and several cancers and Leung et al. pointed out that obesity was a risk factor for pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved LV ejection fraction (Fig. 2).^[22,23] In addition to storing excess calories in the form of lipid, adipose tissue plays an active role in endocrine signaling. Adipocytes generate angiogenic leptin and adipokines and macrophages of the adipose tissue secrete IL-6. Circulating IL-6 levels are correlated with the BMI and adipose tissue is thought to account for 35% of circulating IL-6 in healthy people.^[24] Interactions between IL-6 and estrogen may be important in cancer pathobiology. There is at present no information regarding dietary factors and their potential impact on the lung circulation. Based on strong literature data describing the angiogenic role of copper, a recent study explored copper deficiency and found that a Cu⁺⁺-depleted diet prevented the development of angioobliterative PAH in the Sugen/chronic hypoxia rat model.^[25]

VITAMIN D AND PARATHYROID HORMONE

Vitamins and vitamin deficiency states may also have to be included in the list of modifiers of pulmonary vascular diseases although potential connections between

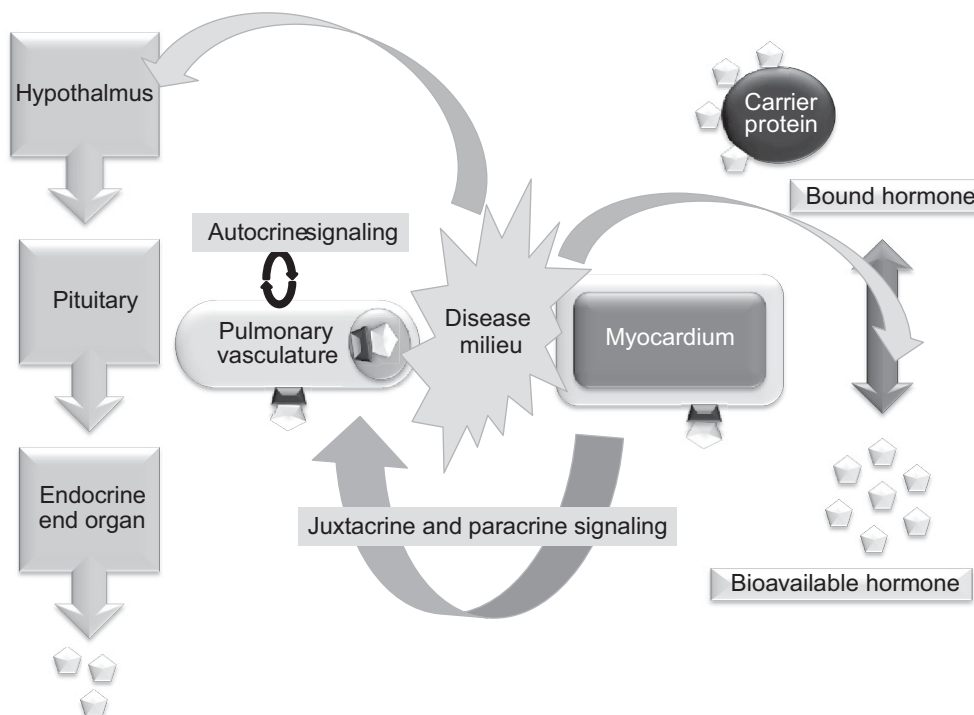


Figure 1: Overview of a general concept of the participation of the endocrine system in pulmonary hypertension and right heart failure. Hormones can be transported by carrier proteins to sites of paracrine signaling receptors or act as in an autocrine fashion. The “sick lung circulation” releases factors which act upon the myocardium [reprinted with permission].^[18]

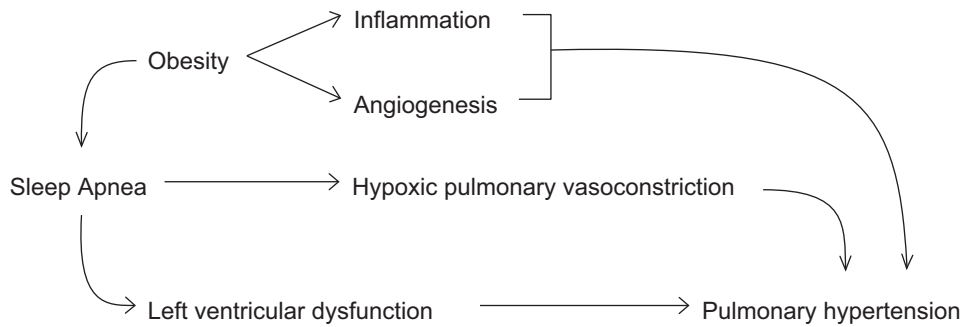


Figure 2: This diagram illustrates the connections between obesity, left ventricular dysfunction and pulmonary hypertension which can be pulmonary arterial or pulmonary venous hypertension.

vitamin deficiencies and pulmonary hypertension remain unexamined. Vitamin D deficiency is a very frequent finding; in fact it has been reported that up to 90% of U.S. adults aged 50–70 are Vitamin D deficient.^[26] Vitamin D is important as a controller of cell growth and regulator of immune functions.^[27–29] Vitamin D may have an angioproliferative role in cancer mediated via HIF-1 α .^[30] Calcitriol (1,25[OH₂] D₃), the active form of Vitamin D, reduces the expression of VEGF and also endothelin.^[30] Vitamin D deficiency was found in 49% of patients with the antiphospholipid syndrome and Ulrich et al. described secondary hyperparathyroidism in patients with pulmonary hypertension;^[31] they suggest that the hyperparathyroidism is a consequence of vitamin D deficiency.^[32] Parathyroid hormone (PTH) elevation may mobilize bone marrow-derived progenitor cells comparable to the effect of G-CSF.^[33] PTH increases mesenchymal stem cell proliferation and stimulates VEGF expression in HUVEC.^[34,35]

ESTROGEN

In recent years the “female pulmonary hypertension factor” has received recognition and investigators have begun to develop hypotheses which address the roles of sex hormones in the pathogenesis of pulmonary hypertension. PAH develops in young and in menopausal women; young women have high levels of circulating estrogen, while middle-aged women had a high cumulative exposure to estrogen and/or to estrogen replacement therapy. Sweeney et al. surveyed female patients with PAH and reported that 80% of the women had prior use of hormone therapy whether estrogen is a risk factor for the development of PAH is not clear.^[9] It is also not clear whether mechanistically an imbalance between pro- and antiangiogenic estrogen metabolites is important, and whether estrogen receptors are involved remains unresolved.^[18] However, any mechanistic model of sex steroid hormone impact on the lung circulation and lung vascular remodeling should consider an imbalance between androgens and estrogens. Sweeney et al. had collected serum samples from 70 patients with severe PAH and 18 normal control women and analyzed the samples

for estrogen metabolites, using mass spectroscopy. This single time point analysis showed that patients of this PAH cohort had a relative 17- β -estradiol deficit when compared to age-matched control women.^[36] To the degree that estrogen has cardioprotective effects this deficit may put women with PAH at a disadvantage.

THYROID DISEASE

The pulmonary hypertension group at the University of Colorado brought attention to an association of PAH with hypothyroidism.^[12] Subsequently other investigators around the world have confirmed this association.^[9,13–15] More recently an association between pulmonary hypertension and hyperthyroid conditions, in particular Graves disease and multinodular goiter, have been reported (Table 1).^[37–42] In addition, there are several case reports of the development of hyperthyroid disease in patients with idiopathic PAH after treatment with prostacyclin. Remarkably there is no formulated hypothesis which provides a mechanistic explanation for these associations. Given the overlap between PAH and autoimmune diseases, hypothyroidism in patients with PAH is commonly considered a consequence of an autoimmune thyroiditis – as another manifestation of a still ill-defined underlying immune dysregulation. It is intriguing to speculate that in the lung and in the thyroid gland a common denominator is a disease of the microcirculation: the thyroid gland is hypervascularized in Graves disease but hypovascularized in Hashimoto thyroiditis.^[43] Thyroid hormones can affect the cardiopulmonary system by increasing heart rate and blood flow through the lung. Pulmonary hypertension in Graves disease is in part due to a high cardiac output. Because thyroid hormones stimulate endothelial cell growth^[44], we hypothesized that thyroid hormones can also contribute to the development of pulmonary hypertension by promoting angioproliferation. We therefore assessed the contribution of thyroid hormones to pulmonary vascular remodeling in the Sugen / chronic hypoxia rat model of severe PAH. The results of this study were published recently^[45] and here we recapitulate the main findings of this study.

Table 1: Hyperthyroidism and pulmonary hypertension in clinical trials and case reports

Number of patients	Diagnosis	Hyperthyroidism diagnosis before PH diagnosis	PASP before hyperthyroidism treatment (mmHg)	PASP after hyperthyroidism treatment	Improvement after treatment	Authors (references)
114 (43% with PH)	47 = Graves; 67 = MNG	Yes	27±6 (e)	<25 (e) (4 weeks)	Yes	Marvisi et al.
75 (46% with PH)	30 = Graves; 35 = MNG	Yes	48±1.2 (e)	34±2 (e) (24 weeks)	Yes	Siu et al.
47 (34% with PH)	Hyperthyroidism (unspecified)	Yes	26±12 (e)	23±10 (e) (12 weeks)	Yes	Guntekin et al.
33 (41% with PH)	Hyperthyroidism (unspecified)	Yes	36±12 (e)	29±8 (e) (56±32 weeks)	Yes	Mercé et al.
23 (65% with PH)	22 = Graves; 1 = MNG	Yes	36±8 (e)	26±5 (e) (36 weeks)	Yes	Armigliato et al.
25 (44% with PH)	7 = Graves; 18 = MNG	Yes	30±8 (e)	24±5 (e) (24 weeks)	Yes	Yazar et al.

e: echocardiography; PH: pulmonary hypertension; MNG: multinodular goiter

THE SUGEN/CHRONIC HYPOXIA MODEL OF PAH

This model is based on the combination of chronic VEGF receptor blockade and chronic hypoxia. The underlying concept is that two hits are required to generate severe angioobliterative PAH in the rat: Sugen 5416 (semaxinib) binds with high affinity to the intracellular tyrosine kinase part of VEGFR1 (flt1) and VEGFR2 (KDR) and thus inhibits the signal transduction of these two receptors while chronic hypoxia increases the resistance to blood flow via pulmonary vasoconstriction. Sugen 5416-induced VEGFR blockade causes loss of alveolar septal cells by inducing lung endothelial cell apoptosis.^[46,47] These emphysematic changes are accompanied by mild PAH.^[46] Chronic hypoxia, in addition to causing an increase in pulmonary vascular shear stress, also activates inflammatory mechanisms and causes homing of precursor-or stem cells to the lung.^[48,49] We showed in our original description of this two-hit-model of PAH that the Sugen 5416-induced pulmonary endothelial cell apoptosis is necessary for the subsequent development of angioproliferation and Sakao et al. showed in a cell model of HUVEC subjected to high flow shear stress that Su5416 induced HUVEC apoptosis followed subsequently by lumen-filling proliferation of the HUVEC that had survived the initial apoptosis.^[50,51] It is probably of interest and worth mentioning that umbilical cord endothelial cells are fetal cells which contain also pluripotent precursor cells. The pulmonary arteriolar lesions in this model have been characterized to some extent and Abe et al. have reported that with passage of time these lesions resemble the plexiform lesions in the lungs from patients with severe PAH.^[52,53] The animals treated with Sugen 5416 and exposed to hypoxia for 4 weeks develop right heart failure and the PAH is refractory to treatment.^[54-56]

THE ROLE OF THYROID HORMONE IN THE SUGEN/HYPOXIA MODEL OF PAH

To address the question whether thyroid hormones contribute to the formation of the pulmonary angioobliteration we subjected in the first set of experiments thyroidectomized male rats to the standard Sugen/chronic hypoxia protocol.^[45] Subtotal thyroidectomy decreased plasma thyroxine (T4) to about 20% of the levels in non-thyroidectomized animals. The animals also had a lower heart rate and a lower cardiac output when compared to the Sugen/chronic hypoxia animals – and importantly the mean pulmonary artery (mPAP) approached the mPAP observed in normal control rats not treated with Sugen or exposed to hypoxia (Fig. 3). Whereas approximately 40% of the precapillary arterioles were completely obliterated in the Sugen/chronic hypoxia animals only 8% of these vessels were obliterated in the thyroidectomized Sugen/chronic hypoxia animals (Fig. 4).^[45]

We next implanted T4 pellets s.c. in thyroidectomized rats in order to prove that indeed it was lack of the thyroid hormone that had prevented the pulmonary vasoobliteration. The T4-reconstituted thyroidectomized rats were then subjected to the standard Sugen/chronic hypoxia animal. These animals had slightly higher plasma levels of T4 than the normal control rats and when exposed to sugen and chronic hypoxia the degree of pulmonary hypertension was indistinguishable from that of nonthyroidectomized Sugen/chronic hypoxia rats; however, the number of fully obliterated lung vessels was smaller than in the nonthyroidectomized Sugen/hypoxia rats. Thus, in the aggregate the data support the conclusion that thyroid hormone plays a role in the development of angioproliferative PAH in this model. Next we used a different and pharmacological approach and inhibited T4 production in the rats with propylthiouracil (PTU). This treatment reduced plasma T4 hormone levels, and

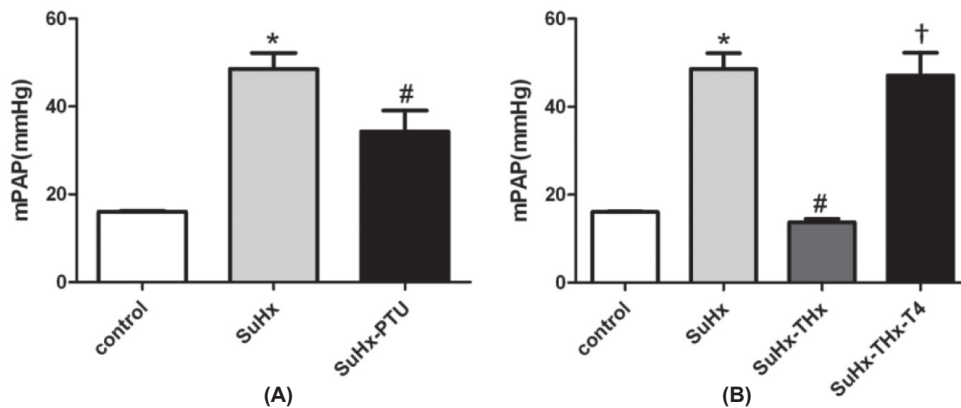


Figure 3: The effect of propylthiouracil (PTU) treatment or thyroidectomy (THx) on the mean pulmonary arterial pressure (mPAP) of rats exposed to the Sugen 5416/chronic hypoxia (SuHx) protocol. The mPAP was measured in anesthetized rats. Both PTU treatment and thyroidectomy reduced the mPAP. One group of the thyroidectomized animals exposed to the SuHx protocol had thyroxine (T4) pellets implanted at the onset of the 4 weeks chronic hypoxia (SuHx-THx-T4). * $P < 0.05$ different when compared with euthyroid controls. # $P < 0.05$ different when compared with SuHx animals.

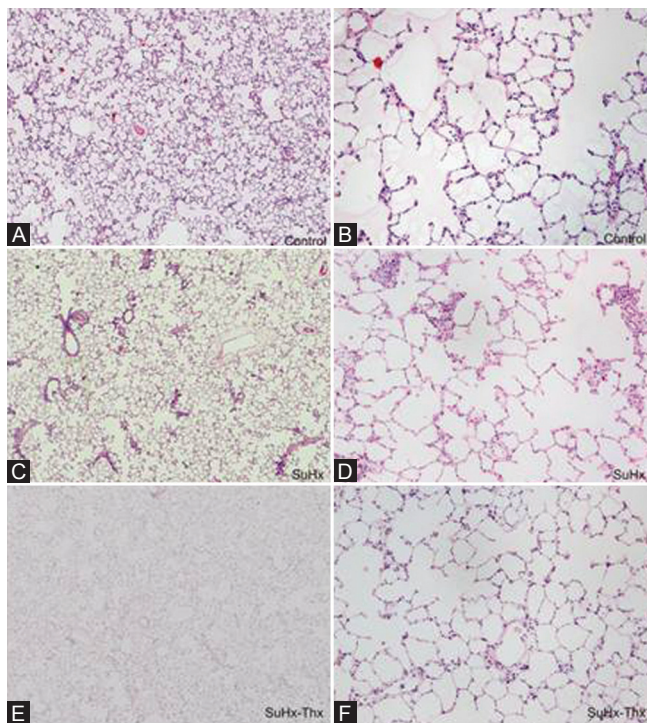


Figure 4: Lung tissue sections (HE staining) from an euthyroid normal control rat lung (A), higher magnification (B) a lung tissue section from a rat treated with Sugen 5416 and exposed to chronic hypoxia for 4 weeks (C, D) and a thyroidectomized rat exposed to Sugen 5416 and chronic hypoxia (E, F). In animals with a partial thyroidectomy no angioproliferative lesions were observed.

reduced the mPAP in Sugen/chronic hypoxia animals and the number of fully obliterated pulmonary arterioles. There was a positive correlation between the RVSP and the number of obliterated vessels. Thus the PTU treatment data support the data obtained with thyroidectomized rats. Important control experiments were performed to find out whether thyroid hormone per se was sufficient to cause pulmonary angioproliferation: rats were injected with Su5416 (but not exposed to hypoxia) and T4 pellets were implanted s.c. and the animals were studied at four weeks after continuous T4 treatment.^[45] Because the combination

of Su5416+T4 did not cause angioproliferation, we conclude that T4 in the Sugen/chronic hypoxia model is permissive and that Su5416-induced lung cell apoptosis by itself without accompanying hypoxia is not sufficient as a driver of exuberant T4-induced endothelial cell proliferation.

PUTATIVE MECHANISM OF THYROID HORMONE RELATED PULMONARY ANGIOBLITERATION IN THE RAT MODEL OF PAH

Thyroid hormones activate membrane- and nuclear receptor pathways. Davis et al. described in elegant studies endothelial cell growth stimulated by T4 via the $\alpha v \beta_3$ integrin and signaling via ERK1/2 and STAT3.^[44,57-59] T4 can activate VEGF production as well as FGF-2 production. Because in the Sugen/chronic hypoxia model two of three VEGF receptors are blocked, we wondered whether the T4-associated pulmonary angioproliferation could occur with the participation of the $\alpha v \beta_3$ /FGF-2/ERK1/2 signaling. Indeed, using IHC we could show a strong expression of $\alpha v \beta_3$, FGF-2, FGF-receptor and ERK1/2 proteins in the vasoobliterative lesion cells – these signals were not expressed in the thyroidectomized Sugen/chronic hypoxia rats.^[45] These results provide the first hint that signaling via the integrin $\alpha v \beta_3$ and FGF receptors may participate in the formation of the lung vascular lesions in this model of PAH. Experiments are underway to target these proteins using blocking antibodies.

CONCLUSIONS

As the WHO classification of PH illustrates, PAH is multifactorial and it is almost certain that in addition to the known genetic factors like BMPR2 mutations mediators of inflammation, immune system abnormalities and a host of epigenetic factors shape the pulmonary vascular disease in the individual patient.^[1] Whether and how female factors,

obesity and the metabolic syndrome modify PH is under intense investigation. Gender plays an important role in the pathobiology of heart diseases. The incidence of heart disease increases in women after menopause indicating that sex hormones play an important role in the development of heart disease.^[60] This general statement likely applies to the right ventricle when under pressure in PAH.^[19] Estrogen can be angioproliferative and protects cardiac myocytes against apoptosis.^[60] As much as estrogen may enhance the process of pulmonary angioproliferation it may protect the myocardium of the right ventricle under pressure. To what extent thyroid hormones affect the pulmonary vascular/right heart axis in PAH is understood only in part in the clinical setting of hyperthyroidism, with its dramatic manifestations of tachycardia and increased cardiac output. A more complex situation presents itself when hyperthyroidism is associated with PAH. We have illustrated in a relevant animal model of severe PAH that thyroid hormone, via its endothelial cell-proliferative action, can be permissive and drive angioproliferation.^[45] Whether thyroid hormones in euthyroid PAH patients play a pathobiologically important role is unknown – as we also do not know whether the commonly diagnosed hypothyroidism in patients with severe PAH is cardioprotective.

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