Pulmonary arterial hypertension and thyroid disease*

Hipertensão arterial pulmonar e doenças da tireoide

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Abstract

Recent studies have suggested an association between pulmonary arterial hypertension (PAH) and thyroid diseases (hypothyroidism and hyperthyroidism). This combination has a good prognosis, because the increase in the pulmonary artery pressure is usually slight and reverses after the treatment of the thyroid disease. Although the exact mechanism involved in the pathogenesis of this combination has not yet been established, it has been hypothesized that thyroid hormones and autoimmunity have a direct influence. Due to the high prevalence of thyroid disease in patients with PAH, thyroid function tests should be considered in the investigation of every patient with PAH. In this review, we describe the prevalence of PAH in patients with thyroid diseases and the prevalence of thyroid disease in patients with PAH, as well as addressing the principal effects that thyroid diseases have on the respiratory system. In addition, we report the treatment effects in patients with these diseases.

Keywords: Hypertension, pulmonary; Graves disease; Hyperthyroidism; Hypothyroidism; Thyroid hormones; Echocardiography.

Resumo

Estudos recentes têm sugerido uma associação entre hipertensão arterial pulmonar (HAP) e tireoidopatias (hipotireoidismo e hipertireoidismo). Esta associação tem um bom prognóstico, porque o aumento na pressão da artéria pulmonar geralmente é leve e reversível com o tratamento da tireoidopatia. O mecanismo exato envolvido na patogênese desta associação não está estabelecido, e a influência direta dos hormônios da tireoide e a autoimunidade são consideradas como hipóteses. Devido à alta prevalência de doenças da tireoide em pacientes com HAP, testes de função tireoidiana devem ser considerados na investigação de todo paciente com HAP. Neste artigo de revisão, descrevemos a prevalência de HAP em pacientes com doenças da tireoide e a prevalência de tireoidopatias em pacientes com HAP, assim como destacamos os principais efeitos das doenças da tireoide no sistema respiratório. A seguir, relatamos os efeitos do tratamento destas patologias.

Descritores: Hipertensão pulmonar; Doença de Graves; Hipertireoidismo; Hipotireoidismo; Hormônios tireóideos; Ecocardiografia.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is characterized by a sustained increase in pulmonary artery pressure and a progressive increase in pulmonary vascular resistance, leading to right ventricular insufficiency and premature death.[1] Classically, pulmonary hypertension was divided into primary (idiopathic) and secondary forms. However, within the secondary PAH category, there are conditions that are similar to those of primary PAH, in terms of histopathological characteristics as well as response to treatment. The World Health Organization has periodically offered classifications of PAH, the current classification being the result of a consensus meeting held in 2003 in Venice, Italy (Chart 1).[1-3] A new classification is expected in 2008.

Mean pulmonary artery pressure (MPAP), under physiological conditions and at sea level, is ≤ 20 mmHg, and pulmonary artery systolic pressure (PASP) is ≤ 30 mmHg. The definition

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of PAH (group 1 of the Venice Classification; Chart 1) is based on hemodynamic criteria: MPAP > 25 mmHg at rest or > 30 mmHg during exercise, with pulmonary capillary pressure or left atrial pressure < 15 mmHg and pulmonary vascular resistance > 3 mmHg • L^{-1} • s^{-1} or 240 dynes • s^{-1} • cm^{-5}.[2,3]

The principal alterations seen in PAH are vasoconstriction, remodeling and in situ thrombosis. There is endothelial dysfunction, which leads to impaired production of vasodilators, such as NO and prostacyclin, and increased expression of vasoconstrictors and mitogens, such as endothelin-1.[1]

Idiopathic PAH is more common in women than in men (ratio, 1.7:1), and the mean age at diagnosis is 36 years. In many cases, the diagnosis of PAH is delayed, since the symptoms are nonspecific and can be confused with those of other, more common diseases. Dyspnea is the initial symptom in 90% of patients. Less common symptoms include fatigue, chest pain, syncope, peripheral edema and palpitations.[4]

Various diseases, such as portal hypertension, hemoglobinopathies, collagen diseases and HIV infection, are associated with PAH. Recent studies have suggested an association between PAH and thyroid diseases (hypothyroidism and hyperthyroidism).[6-23] Since the Third World Conference on Pulmonary Hypertension, held in 2003, thyroid diseases have been classified as diseases associated with PAH.[2] However, although some pathogenic mechanisms have been proposed, the nature of this association has not yet been established (Chart 2).

In this review, we describe the prevalence of PAH in patients with thyroid diseases and the prevalence of thyroid disease in patients with PAH, as well as addressing the principal effects that thyroid diseases have on the respiratory system. In addition, we report the treatment effects in patients with these diseases.

Chart 1 - Clinical classification of pulmonary hypertension established at the consensus meeting held in 2003 in Venice, Italy.[1,2]

Group 1. Pulmonary arterial hypertension
Idiopathic (primary)
Familial
Associated with: collagen vascular disease, congenital systemic-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins (anorectic drugs, L-tryptophan, methamphetamine, cocaine); others: thyroid disease, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy.
Associated with significant capillary or venous involvement
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Group 2. Pulmonary venous hypertension
Left ventricular or left atrial heart disease
Left valvular heart disease
Group 3. Pulmonary hypertension accompanied by hypoxemia
COPD
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation
Chronic exposure to high altitudes
Growth-related abnormalities
Group 4. 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 (tumor, parasites, foreign body)
Group 5. Miscellaneous
Sarcoidosis, Langerhans cell histiocytosis, lymphangioleiomyomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Chart 2 - Possible pathogenetic mechanisms involved in the combination of pulmonary arterial hypertension and thyroid disease.

Hyperthyroidism
Autoimmune phenomenon associated with endothelial damage or dysfunction
Increase in cardiac output resulting in endothelial damage
Increased metabolism of intrinsic pulmonary vasodilators (prostacyclin and NO)
Decreased metabolism of vasoconstrictors (serotonin, endothelin-1 and thromboxane)
Stimulation of the sympathetic nervous system, causing pulmonary vasoconstriction
Hypothyroidism
Autoimmune phenomenon associated with endothelial damage or dysfunction
Vascular reactivity caused by a decrease in the levels of thyroid hormone (vascular stabilizing effect of the thyroid hormone)
Inflammation

Prevalence of PAH in patients with thyroid diseases

In a study that evaluated patients recently diagnosed with hyperthyroidism, the prevalence of PAH was found to be 35%.[9] In another study, involving 114 patients with hyperthyroidism (47 with Graves' disease and 67 with multinodular goiter), the prevalence of PAH was found to be 43%.[10] In those two studies, a diagnosis of PAH was made when PASP, as estimated by echocardiography, was > 30 mmHg.

In other studies, a diagnosis of PAH was made when PASP, as estimated by echocardiography, was > 35 mmHg. In a study involving 39 consecutive patients recently diagnosed with hyperthyroidism, the prevalence of PAH was found to be 41%.[11] In another study, involving 23 patients with hyperthyroidism (Graves' disease or multinodular goiter), the authors found a prevalence of PAH of 65%.[12] The prevalence of PAH in a cross-sectional study that investigated 20 patients with hyperthyroidism (under treatment with antithyroid drugs or not) was 50%.[13] In a prospective study that described the echocardiographic findings in 75 consecutive patients with hyperthyroidism, the prevalence of PAH was 47%.[14] The principal characteristics of those studies are described in Table 1.

In a review of the literature, we found no studies evaluating the prevalence of PAH in patients with hypothyroidism, this combination being described only in case reports.

Prevalence of thyroid disease in patients with PAH

In a prospective study, 63 consecutive patients with PAH (MPAP > 25 mmHg at rest, as estimated by right heart catheterization) were evaluated regarding the presence of autoimmune thyroid disease (AITD): Hashimoto's thyroiditis; Graves' disease; and euthyroidism in the presence of antithyroid antibodies.[15] The authors found the prevalence of AITD in the patients with PAH to be 49%.

In a retrospective study, the prevalence of hypothyroidism in 41 patients with PAH (MPAP > 25 mmHg at rest, as estimated by right heart catheterization) was found to be 22.5%.[7] In another study, a sample of 356 patients with PAH and 698 gender-matched controls without PAH were retrospectively evaluated. Of the patients with PAH, 85 (24%) had thyroid disease, as did 107 (15%) of the controls. Most patients had mild thyroid disease, predominantly hypothyroidism.[16] The principal characteristics of those studies are described in Table 1.

Effects that hyperthyroidism and hypothyroidism have on the respiratory system

The cardiac disorders caused by thyrotoxicosis can affect the lungs in two ways: high-deficit heart failure or dilatation of the pulmonary artery, possibly accompanied by PAH. Slight increases in pulmonary artery pressure at rest are common in patients with thyrotoxicosis, and the pressure usually increases significantly during exercise. However, the potential for severe PAH attributable to thyrotoxicosis alone remains unclear.[5] The cases described are mainly related to hyperthyroidism of autoimmune origin (Graves' disease).

The possible pathogenetic mechanisms suggested for the combination of PAH and Graves' disease are the following: autoimmune phenom-

Table 1 - Principal characteristics of studies that evaluated the prevalence of pulmonary arterial hypertension in patients with thyroid diseases and the prevalence of thyroid disease in patients with pulmonary arterial hypertension.

Study	Year	n of patients	Definition of PAH (echocardiography)	Prevalence of PAH
Marvisi et al.[9]	2002	17	PASP > 30 mmHg	35%
Mercé et al.[11]	2005	39	PASP > 35 mmHg	41%
Marvisi et al.[10]	2006	114	PASP > 30 mmHg	43%
Armigliato et al.[12]	2006	23	PASP > 35 mmHg	65%
Pires et al.[13]	2006	20	PASP > 35 mmHg	50%
Siu et al.[14]	2007	75	PASP > 35 mmHg	47%
Study	Year	n of patients	Definition of PAH (catheterization)	Prevalence of thyroid disease
Curnock et al.[7]	1999	41	MPAP > 25 mmHg	22.5% hypothyroidism
Chu et al.[15]	2002	63	MPAP > 25 mmHg	49% AITD
Li et al.[16]	2007	356	MPAP > 25 mmHg[a]	24% hypothyroidism

PAH: pulmonary arterial hypertension; PASP: pulmonary artery systolic pressure; MPAP: mean pulmonary artery pressure; and AITD: autoimmune thyroid disease. [a]In the Li et al. study, 65% of the patients underwent right heart catheterization; in the remaining patients, MPAP was estimated by echocardiography.

enon associated with endothelial damage or dysfunction; increased cardiac output, resulting in endothelial damage; and increased metabolism of intrinsic pulmonary vasodilators.[6]

Nevertheless, hypothyroidism is associated with respiratory disorders such as hypoventilation and hypoxia, and these disorders can worsen the concomitant PAH. Thyroid dysfunction has been linked to vascular reactivity, a phenomenon that can precede PAH. Raynaud's phenomenon, which is seen in patients with idiopathic PAH, also occurs in patients with hypothyroidism and can improve with supplementation of thyroid hormone.[7] It is known that PAH and hypothyroidism are associated with various autoimmune diseases, which raises the hypothesis of a common autoimmune pathophysiological mechanism.[8]

Mutations in the bone morphogenetic protein receptor, type 2 (BMPR2) have been reported in patients with idiopathic PAH. Curiously, in a study carried out in order to determine the frequency of those mutations, all 5 patients who presented BMPR2 mutations had thyroid disease. Of those, 4 had thyroiditis, and 1 presented follicular hyperplasia.[23] Further studies are necessary in order to confirm the association between thyroid disease and BMPR2 mutations, as well as to determine the possible associated mechanisms.

Effects that the treatment of the thyroid disease has on PAH

In a study conducted in 1997,[17] 4 cases of hyperthyroidism and concomitant PAH were described. Of those, 3 had Graves' disease, and 1 presented toxic multinodular goiter. The mean pretreatment PASP was 40 ± 11 mmHg. The patients were treated with radioactive iodine or ethionamides. After the treatment, a second echocardiogram was performed (at intervals that ranged from 1 to 6 months), and PASP decreased to a mean of 25 ± 6 mmHg in all patients. Although it has been suggested that there is an autoimmune pathogenetic relationship between PAH and thyroid diseases, in one of the cases reported, the patient had no increased levels of antithyroid antibodies. Therefore, another possible mechanism proposed was the direct influence that thyroid hormones have on the pulmonary vasculature. Various other case reports have suggested an association between PAH and Graves' disease, always with a decrease in and often with the normalization of PASP levels (as estimated by echocardiography or right heart catheterization) after the treatment of the thyroid disease.[6,18-22]

An observational study[9] evaluated 34 patients with hyperthyroidism. Of those, 20 had received a diagnosis of Graves' disease, and 14 had nodular goiter. The patients were divided into two groups: those recently diagnosed with hyperthyroidism, without treatment (17 patients) and those who were euthyroid, under treatment with methimazole (17 patients). In addition, there was a control group (17 patients) consisting of healthy individuals. Mild PAH was present in 35% of the patients in the untreated hyperthyroidism group (mean PASP of 28.88 ± 6.41 mmHg) and in none

of the patients of the two other groups. There was also a strong negative correlation between the levels of thyroid-stimulating hormone (TSH) and PASP (r = −0.82), as well as a positive correlation between thyroxine levels and PASP (r = 0.85), in the patients with hyperthyroidism without treatment.

The same authors, in another study,[10] evaluated the role of methimazole in the regulation of pulmonary vascular resistance in patients with hyperthyroidism and PAH. A total of 114 patients were studied. Those patients were divided into two groups: those treated with methimazole; and those treated with partial thyroidectomy. Patients in both groups were monitored for 120 days. After 15 days of treatment, PASP decreased from 34.3 ± 3.2 mmHg to 29.2 ± 3.3 mmHg in the methimazole group, compared with a decrease from 34.3 ± 3.0 mmHg to 34.1 ± 2.9 mmHg in the partial thyroidectomy group ($p < 0.001$). Previous studies have demonstrated that methimazole can regulate the production of N(G)-nitro-L-arginine methyl ester (L-NAME), an arginine analog, producing acute NO synthesis inhibition, as well as presenting vasoactive properties related to the pulmonary and systemic vasculature.

Increased serum levels of uric acid have been demonstrated in patients with hyperthyroidism, as well as in those with PAH.[24] In the latter, these increased levels are believed to be due to lung tissue ischemia or right ventricular ischemia, whereas, in the former, they are due to the increased production of uric acid, which surpasses its clearance. One study[24] demonstrated that the levels of PASP and uric acid are significantly higher in patients with hyperthyroidism (PASP > 30 mmHg in 44%) than in controls, also decreasing significantly after the treatment. However, there was no correlation between the levels of PASP and uric acid.

Possible effects that the treatment of PAH has on the thyroid

In patients with PAH, there is increased release of the vasoconstrictor thromboxane A2 and decreased release of prostacyclin (prostaglandin I_2—PGI_2).[25] Continuous intravenous infusion of prostacyclin (epoprostenol) as well as inhaled prostacyclin analog (iloprost) are used in the treatment of PAH.[2] Thyroid function tests were requested in a study involving 78 children and 134 adults with PAH.[26] Of the 134 adults, 26 had thyroid disease (hyperthyroidism or hypothyroidism), and 20 of the 26 were under treatment with PGI_2. Of those 20 patients, 11 developed thyroid dysfunction after PGI_2 treatment was started. Thyrotoxicosis developed in 36% of the cases, raising the possibility that PGI_2 treatment can trigger its development. Earlier studies demonstrated decreased levels of PGI_2 receptors and a decreased production of cAMP in the thyroid of patients with Graves' disease, indicating that PGI_2 plays an important role in the modulation of thyroid function.[27,28] Levels of 6-keto-PGF1, a metabolite of PGI_2, are increased in patients with Graves' disease, correlating with triiodothyronine and thyroxine levels and decreasing after treatment with antithyroid drugs.[29] In addition, one group of authors demonstrated that PGI_2 stimulates TSH secretion.[30]

The enzyme responsible for NO formation, NO synthase, is a potent endothelium-derived vasodilator. There is an association between PAH and decreased levels of this enzyme.[31] The administration of L-arginine, an NO synthase substrate, increases the production of NO and has been used in the treatment of PAH. In addition, NO might play a role in the vascular alterations observed in patients with thyroid dysfunction.[32] It is known that NO synthase is present in the follicular and endothelial cells of the human thyroid. The production of NO is decreased in patients with hyperthyroidism.[33]

Sildenafil, a 5-phosphodiesterase inhibitor, initially developed for the treatment of erectile dysfunction, has been used in the treatment of PAH due to its vasodilator properties.[2] A recent study in rats has shown that hypothyroidism or thyroidectomy caused depletion of the endothelium-derived relaxing factor and that the effects of sildenafil on erectile function are only possible in the presence of adequate levels of thyroid hormones.[34]

Endothelin-1 is a potent endothelium-derived vasoconstrictor peptide with important mitogenic properties. There is an association between PAH and increased endothelin-1 expression in vascular endothelial cells.[35] Bosentan, an endothelin-1 receptor antagonist, is used in the treatment of PAH.[2] A study in rats showed that the euthyroid state is necessary in order to maintain the physiological concentrations

of endothelin-1 in the lungs. However, in that study, hypothyroidism and hyperthyroidism were associated with decreased plasma levels of endothelin-1.[36]

Conclusion

The data currently available in the medical literature indicate that PAH and thyroid diseases often occur in conjunction. A significant percentage of patients with PAH (between 35% and 65%, according to the studies available) have concomitant thyroid dysfunction. The increase in PASP usually reverses after the treatment of the thyroid disease The exact mechanism involved in the pathogenesis of this combination has not yet been established, and further studies are necessary. Thyroid function tests should be considered in the investigation of every patient with PAH.

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