Arterial hypertension and thyroid disorders: What is important to know in clinical practice?

Hypertension artérielle et pathologie thyroïdienne : points importants en pratique clinique

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Abstract

This review describes the pathogenic mechanisms of blood pressure (BP) regulation and long-term control in thyroid disorders. Variations from the euthyroid status affect virtually all physiological systems but the effects on the cardiovascular system are particularly pronounced. Thyroid disorders induce several hemodynamic changes leading to elevated BP as a consequence of their interaction with endothelial function, vascular reactivity, renal hemodynamic and renin-angiotensin system. However, in thyroid disorders, the regulation of BP and the development and maintenance of variable forms of arterial hypertension (HT) are different. Hyperthyroidism results in an increased endothelium-dependent responsiveness secondary to the shear stress induced by the hyperdynamic circulation, and contributes to reduce vascular resistance. Conversely,

Abbreviations: BP, blood pressure; HT, arterial hypertension; CCB, calcium-channel blockers; TSH, Thyroid stimulating hormone, thyrotropin; T4, thyroxine; T3, triiodothyronine; CO, cardiac output; SVR, systemic vascular resistance; HR, heart rate; RAAS, renin-angiotensin-aldosterone system; ACE, angiotensin-converting-enzyme; ABPM, ambulatory BP monitoring; SH, subclinical hyperthyroidism; SCH, subclinical hypothyroidism; PRA, Plasma renin activity.

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hypothyroidism is accompanied by a marked decrease in sensitivity to sympathetic agonists with an increase of peripheral vascular resistance and arterial stiffness. Furthermore in animal models, hypothyroidism reduces the endothelium-dependent and nitric oxide-dependent vasodilatation. HT due to thyroid disorders is usually reversible with achievement of euthyroidism, but in some cases pharmacological treatment for BP control is required. In hyperthyroidism, β-blockers are the first-choice treatment to control BP but when they are contraindicated or not tolerated, ACE-inhibitors or calcium-channel blockers (CCB) are recommended. Hypothyroidism is a typical low rennin HT form showing a better antihypertensive response to CCB and diuretics; indeed in hypothyroidism a low-sodium diet seems further to improve BP control. Randomized clinical trials to compare the efficacy on BP control of the antihypertensive treatment in thyroid disorders are needed.

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1. Introduction

Variations from the euthyroid status affect virtually all physiological systems but the effects on BP regulation are particularly pronounced [1,2]. At population level, the relationship between thyroid hormones and the different BP components is not well established. Asvold et al. [3] reported a linear correlation between TSH and both systolic and diastolic BP, whereas other authors did not find this association [4–6]. Conversely, in clinical practice, it is well known that the effects of hyperthyroidism on clinic BP are opposite to those occurring in hypothyroidism [7]. HT is frequently observed both in hyper- and hypothyroidism, suggesting that different mechanisms are involved in these two conditions [2,8]. However, several studies have shown that hyperthyroidism accelerates [9] while hypothyroidism prevents and reverses some models of experimental HT [10] and that HT related to hypothyroidism is reversible after T4 treatment [11]. However, in some cases, a pharmacological treatment with anti-hypertensive drugs to control BP is required.

2. Thyroid hormone effects on blood pressure regulation

BP is the result of the following algorithm: CO × SVR. As a consequence, the effect of thyroid hormones on BP regulation derives particularly from their interaction with these two parameters [12]. However, thyroid hormones influence other hemodynamic items such as HR, cardiac contractility and blood volume (Table 1).

CO is strongly regulated by HR, and because it determines the rate of cardiac ejection, it affects both systolic and diastolic ventricular function [7]. In addition, the effect of HR on myocardial contractility does not increase CO if preload is not increased or at least kept constant. Preload, defined as the volume of blood that remains in the left ventricle at the end of the diastolic phase of cardiac cycle, is the most efficient mechanism by which CO is adjusted to the peripheral metabolic demand, and in normal conditions, it is largely regulated by venous return, which in turn depends on venous tone and SVR.

Conversely, SVR largely regulates the afterload, defined as the hemodynamic force exerted on the ventricular wall during ejection, which in turn depends on global arterial compliance and aortic impedance, which are indices of wave propagation along the arterial system. In detail, SVR are regulated by the activity of the smooth muscle and endothelial cells of the arterial wall. However, the mechanisms by which thyroid hormones affects endothelial cells and vascular tone are poorly understood. Increased capillary density as well as elevated expression of vascular endothelial growth factors has been reported in thyroid disorders. Data obtained in animal experimental models suggest that thyroid hormones exert part of their vascular effect through an endothelium-mediated mechanism and induce the endothelium-independent relaxation stimulating the nitric oxide production from the endothelial cells.

In addition to CO and SVR modulation, thyroid hormones regulate BP by activating RAAS [13]. In particular, thyroid hormones modulate the RAAS influencing plasma rennin activity (PRA), plasma angiotensin II and aldosterone levels. In hyperthyroidism, the RAAS is activated as a compensatory response to the reduced SVR and mean BP. Furthermore, there is evidence that T3 directly stimulates the synthesis of rennin substrate in the liver and enhances the cardiac expression of rennin mRNA, leading to increased cardiac levels of rennin and angiotensin II independently from the circulating RAAS. On the contrary, hypothyroidism is accompanied by decrease of many components of RAAS, including the secretion of rennin, the hepatic production of angiotensinogen, serum ACE activity and the adrenal production of aldosterone. The regulatory effect of thyroid disorders on renal function are shown in Fig. 1.

Juxtaglomerular apparatus is volume and pressure sensitive and the modulation of RAAS cascade in response to the variations in mean arterial pressure contributes to regulate BP levels in the different forms of HT (Fig. 2). Finally, thyroid hormones have proven to be able to upregulate erythropoietin secretion and consequently red blood cell mass, which may also contribute to the increase in total blood volume and BP [14].

3. Hyperthyroidism and blood pressure

The prevalence of HT is nearly three-fold higher in patients with overt hyperthyroidism than in normal subjects. Overt hyper-
thyroidism and thyrotoxicosis are associated with high BP levels [15]. It is estimated that the prevalence of HT with thyrotoxicosis ranges between 20 to 30%, but there are limited studies to confirm these data because HT is a highly frequent condition [2].

T3, the active form of thyroid hormones, dilates resistance arterioles [16] and reduces SVR [17] by the direct relaxation of vascular smooth-muscle cells [18]. In this regard, in some recent studies, the effect of high intravenous doses of T3 on vascular resistance has been investigated, notably within the frame of cardiovascular surgery. The rationale for using thyroid hormones following cardiovascular surgery is primarily to improve cardiac performance rather than to correct hypothyroidism or sick euthyroid syndromes. Treatment with intravenous T3 during the intraoperative and/or postoperative period increases CO and reduces SVR. However, in a recent systematic review including 14 studies, the role of intravenous T3 therapy administered in the postoperative period is controversial [19]. In this review, four studies showed significantly higher cardiac index among patients who received high intravenous doses of T3 6 h after surgery, and three studies showed similar benefits on CO of low intravenous doses of T3 4–6 h after surgery. The remaining studies showed inconclusive results for SVR, HR, pulmonary capillary wedge pressure, new-onset postoperative atrial fibrillation and inotropic effect. In addition, in four studies, there was no difference in hospital mortality after high-dose intravenous T3 administration. However, because the studies of this review included in the main part patients after coronary artery bypass graft or valve surgery, the results of this review may not be generalizable to other patient populations.

HR and cardiac contractility are also modified by hyperthyroidism. HR may increase up to 40% of the basal value and CO may be up to 300% higher in hyperthyroidism than hypothyroidism [19].

Hypertension in hyperthyroid subjects is considered a model of “cardiogenic hypertension” [7], where the increased BP levels are mainly maintained by the increase of CO, which is secondary to the high stroke volume and HR. The effects of thyroid hormones, particularly of T3, in cardiac myocytes are divided in genomic and nongenomic. In genomic effect, T3, after binding to four types of thyroid hormone nuclear receptors, determines the activation of myocytes-specific genes that increase the synthesis of different cardiac proteins associated with cardiac hypertrophy. In the nongenomic effect, the actions of T3 occur rapidly and do not require binding to intranuclear receptors. T3-mediated nongenomic effects include effects on membrane ion channels for sodium, potassium, and calcium and effects on actin polymerization, adenine nucleotide translocator-1 in the mitochondrial membrane, and a variety of intracellular signalling pathways in the heart [20].

However, in experimental studies on animals with hyperthyroidism and HT, anti-hypertensive treatment with ACE inhibitors reduces BP levels but not CO and HR suggesting that the cardiogenic model is not the only factor responsible of HT in hyperthyroidism.

In this respect, high levels of endogenous vasoactive hormones as the anti-diuretic hormone (ADH) and endothelin-1 [21] seem able to maintain high BP levels in hyperthyroid subjects. Furthermore, several evidences indicate that RAAS plays an important role in increasing BP in hyperthyroidism [22].

As discussed above, kidney juxtaglomerular apparatus is sensitive to volume and BP. The reduction of SVR by T3 causes mean BP decrease, which leads to increased renin synthesis and secretion [13]; in hyperthyroidism PRA and plasma levels of angiotensinogen, angiotensin II and aldosterone are directly related to plasma levels of thyroid hormones. Therefore, whereas T3 decreases SVR and afterload, the activation of RAAS cascade determines an increase of blood volume and preload that contributes to the characteristic increase of CO in hyperthyroidism [22]. This hyperactivity of RAAS is in part mediated by the modification of the β-adrenergic activity [23]. In experimental hyperthyroidism, it was observed an increased number of β-adrenergic receptors in the renal cortex [24], and it well known that β-adrenergic stimulation increases renin secretion [25]. In fact, the acute RAAS blockade [26] decreases BP levels and improves renal hemodynamics. Furthermore, long-term administration of ACE-inhibitors prevents T4-induced hypertension [27]; thyroid status also influences baroreflex function and autonomic system regulating both BP and HT [28].

The sum of these hemodynamic changes determines a rise in systolic BP, a decrease in diastolic BP and a parallel increase of the pulsatile component of BP; while mean BP is only marginally decreased (Table 1). The pulsatile component of BP, pulse pressure (PP), is the difference between systolic BP and diastolic BP.
PP is a marker of increased arterial stiffness, which is a condition per se to increase cardiovascular risk [29], most in the elderly. Hyperthyroidism has been documented as a secondary cause of isolated systolic HT (BP ≥ 140/ < 90 mmHg), which is the most common form of HT and pulse HT in this form of thyroid disorder [2].

Other than clinic measurement of BP by sphygmomanometer, ABPM over 24 h is used increasingly to record BP, but little data are available about its use in subjects with hyperthyroidism [30]. A reduction in nocturnal BP fall was observed in hyperthyroid hypertensive subjects (HTs) as compared with normotensive subjects [31]. One study has shown a similar average 24 h BP in normotensive patients with mild hyperthyroidism compared with normotensive euthyroid subjects [32]. However, whether a blunted nocturnal decline of BP in hyperthyroidism increases target organ damage or cardiovascular risk remains controversial [33].

4. Subclinical hyperthyroidism

Endogenous SH, defined by normal circulating levels of free T4 (FT4) and T3 (FT3) and low levels of TSH, is a common clinical entity and is typically caused by the same conditions that cause overt hyperthyroidism [34]. The diagnosis of SH derives from laboratory and not from clinical signs. SH is characterized by a low or undetectable concentration of serum TSH with both FT3 and FT4 levels within laboratory reference ranges. The cardiovascular risk of SH is related to short-term effects (transition to overt hyperthyroidism) due to the electrophysiological role of thyroid hormones, and to long-term effects of thyroid hormones resulting from increased left ventricular mass and increased cardiac workload.

While evidence for an increased risk of HT in overt hyperthyroidism is well known, the relation between SH and high BP levels has not been established yet. SH was found to be an independent risk factor for atrial fibrillation and left ventricular hypertrophy in patients with other pre-existing cardiac risk factors as HT [35]. However, in a community-based study, it was recently observed that SH is not associated with changes in BP or incidental HT [7]. Consequently, in clinical practice, it is common opinion that SH is not linked to high BP values or HT.

5. Hypothyroidism and blood pressure

After renovascular HT, hypothyroidism is recognized as the second more important form of secondary HT, but it is often ignored or overlooked. In hypothyroid subjects from the general population, the prevalence of HT varies widely from 1 to 50% [4–6,36]. This is due to the different criteria used to define both hypothyroidism and HT, and on the age of the subjects analysed [37,38]. Like other forms of secondary HT, hypothyroidism increases with age and its prevalence is higher in people aged more than 60 years of age, most in women.
The mechanism of HT in hypothyroidism remains unknown. Two factors contribute to HT in overt hypothyroidism: the increases in SVR and arterial stiffness [39–41]. The remarkable vasoconstriction due to increase in SVR, which is the most important mechanism leading HT [7], may reflect the absence of the vasodilator T3 effects on vascular smooth muscle [42], the increase in sympathetic nervous system and the decreased density of vascular β-adrenergic receptors [9]. The reduction on β-adrenergic activity leads to a parallel increase of α-adrenergic response which probably explains the increased SVR and HT of hypothyroid subjects.

The second and more recently documented mechanism leading HT is the increase in arterial stiffness, which likely results from myxedema of the arterial wall [43]. In these respects, a significant increase of brachial-ankle pulse wave velocity, a parameter of arterial stiffening found to be an independent predictor of coronary heart disease, has been observed in SCH [44].

However, the increase in sympathetic nervous system partially explains the pathogenesis of HT in hypothyroid patients. In fact, in hypothyroidism, there is an increase in total body water with a relative decrease in intravascular volume and hypoaemia [45]. The free water retention probably results from two principal mechanisms: a reduction of the glomerular filtration rate limited to the distal diluting segment [46] and of reduction of renal blood flow [47] and an inappropriate secretion [48] of ADH. In hypothyroidism ADH is mildly increased but its levels improve after T3 therapy [49].

Thyroid hormones may also alter red blood cell sodium content and transport [50]. This in part achieved by altering the lithium–sodium (Li–Na) counter-transport mechanism, which also has functional important role in regulating sodium transport in vascular smooth muscle and in the kidney. Essential HT is associated with increased red blood cell Li–Na counter-transport [51] and the same was observed in hypothyroidism [52]. In particular, this alteration alters sodium transport and water metabolism that determines a volume overload and HT.

Instead on hyperthyroidism, hypothyroidism is often accompanied by a rise in diastolic BP and because CO is low, the PP component of BP is narrowed (Table 2). However, in patients with hypothyroidism, both systolic and diastolic BPs are elevated but the severity of this thyroid disorder seems to correlate with the increase in diastolic BP. In elderly HTs, the onset of hypothyroidism may be unrecognized for a long period, and the presence of high diastolic BP represents an important clinical sign on suspicion of hypothyroidism because in this class of age systolic HT is typically predominant. In addition, more than one-half of hypothyroid HTs display low PRA [53] and low angiotensin levels [54] leading to a salt-sensitive form of HT [55].

Another possible mechanism that links hypothyroidism with HT is overweight or obesity. In particular, it was reported that hypothyroid subjects with overweight or obesity had 24 h ABPM values higher than normal healthy volunteers [56]. Kotsis et al. [57] found that hypothyroidism is an important predictor of higher mean 24 h systolic BP, 24 h PP and 24 h systolic BP variability, parameters of ABPM notoriously associated with higher cardiovascular target organ damage.

6. Subclinical hypothyroidism

The role of SCH in cardiovascular disorders is a matter of debate and controversy, in particular as concerning its relationship with HT. In the past few years, several population-based studies have been investigating the association of SCH with BP and HT [4,5,34]. In one of these studies, subjects with SCH had a 2.8-fold increased risk of HT compared to euthyroid subjects [36]. Other studies however, did not found any association [4,5]. The prevalence of SCH range from 5 to 15% of the general population and the mechanisms leading HT are similar to those previously described for the overt hypothyroidism.

In clinical practice SCH, a condition characterized by the presence of normal levels of thyroid hormones with high TSH values, and with few or absent clinical signs and symptoms of thyroid disorders, has been associated with higher diastolic BP [34]. Moreover, it has been recently observed that in women with SCH, the prevalence of HT was significantly higher than in those with normal thyroid hormones [58]. However, after T4 treatment, both diastolic [19] and mean BP [57] may be reduced. Consistent with this finding, the results of two population-based studies [5,59] indicate a positive association between SCH and systolicdiastolic BP.

In hypothyroid subjects, T4 treatment was able to reduce BP and also arterial stiffness [60] and vascular resistance [10]. It has also been shown that thyroid hormones may have direct vasodilator effects on vascular muscle cells [40] and that endothelial dysfunction may be more prevalent in hypothyroid patients [61] and in people with TSH at the upper limit of the normal reference range [62]. In a study of families with high prevalence of HT, concentrations of TSH tended to be in the

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upper limit of the reference range [63], suggesting that certain genetic variants as polymorphism of TSH receptor and type 2 iodothyronine deiodinase genes may affect BP regulation and serum T3 concentration [64]. It is important to remember that instead on hyperthyroidism, hypothyroidism remains unnoticed for a long time therefore representing a real potential cardiovascular risk factor. However, there are currently no evidence for a treatment benefit of subjects with SCH. The most reported studies are observational and there is no agreement on the fact that treatment of SCH is able to reduce the risk of cardiovascular disease and mortality. Large clinical trials with a long follow-up period are needed to elucidate this aspect.

7. Anti-hypertensive treatment in thyroid disorders

HT secondary to thyroid dysfunctions is usually reversible with the achievement of euthyroidism [65]. This finding would encourage the routine assessment of thyroid function in all patients with pre-existing HT that becomes resistant to pharmacological treatment. However hypertension may not resolve immediately when normalization of serum T4, and moderate to severe HT should be treated also with antihypertensive drugs (Table 3).

The treatment of isolated systolic BP in hyperthyroidism should be taken into great consideration because of its impact on coronary heart disease, stroke, heart failure, end-stage renal disease and total mortality [2]. In this setting, antihypertensive therapy with β-adrenergic receptor blockers reduce BP but also ameliorate many of the symptoms of hyperthyroidism, including palpitations, tachycardia, tremulousness, tremor and anxiety [66]. Commonly, propranolol at high doses (above 160 mg daily) is recommended because of its central nervous system penetration. Propranolol slowly decreases serum T3 concentrations up to 30% by inhibition of the 5′-monodeiodinase, enzyme that converts T4 to T3. However, the effect of propranolol occurs over 7 to 10 days, and it gives a little contribute to the therapeutic effects on BP. Subjects with relative contraindications to β-blockade may better tolerate β1-selective drugs such as atenolol or metoprolol. Atenolol, with a starting dose of 25 to 50 mg daily and in increasing dose up to 200 mg daily, similarly causes minimal reductions in serum T3 concentrations, whereas sotalol and nadolol do not show any effect.

In hyperthyroidism, CCB such diltiazem or verapamil are used when β-blockers are contraindicated or not tolerated. These drugs may be extremely useful as adjunctive therapy for hyperthyroidism, while isolated systolic and pulse HT are the most common forms of HT in hyperthyroidism, particularly in the elderly. In addition, a significant rise of systolic and diastolic BP values related to arterial stiffness were observed in SCH. Treatment of thyroid disorders usually lowers BP, but in some cases a pharmacological treatment with anti-hypertensive drugs is required. In hyperthyroidism, β-blockers are the first-choice treatment to control BP but when they are contraindicated or not tolerated ACE-inhibitors or CCB should be used. Hypothyroidism is a typical low-renin form of HT showing a better antihypertensive response to CCB and diuretics; in hypothyroidism a low-sodium diuretic+++
Calcium channel blocker ++ +
β-blocker – ++
Diuretic ++ +
α-blocker ++ –

Table 3
Pharmacological antihypertensive treatment recommended in thyroid disorders.

In conclusion, HT is more common in thyroid disorders. Whether this association is able to influence the risk of cardiovascular disease should be tested in prospective population-based studies. In clinical practice, BP measurement is essential for the global management of thyroid disorders, but in the current jointed guidelines of the European Society of Hypertension and Cardiology, there are no specific recommendations about the management of BP alteration induced by thyroid disorders [68]. However in light of the evidences of the literature, other than ambulatory measurement of BP by sphygmomanometer, the uses 24 h-ABPM is recommended for the diagnosis, management and prognosis of BP alterations induced by thyroid disorders. Regarding prognosis, 24 h-ABPM is essential to evaluate the BP load, circadian variation of BP, ambulatory PP and BP variability: all these parameters are considered surrogate measures to predict target organ damage and risk of cerebrovascular and cardiovascular events.

Systo-diastolic HT is a typical feature of hypothyroidism, while isolated systolic and pulse HT are the most common forms of HT in hyperthyroidism, particularly in the elderly. In addition, a significant rise of systolic and diastolic BP values related to arterial stiffness were observed in SCH. Treatment of thyroid disorders usually lowers BP, but in some cases a pharmacological treatment with anti-hypertensive drugs is required. In hyperthyroidism, β-blockers are the first-choice treatment to control BP but when they are contraindicated or not tolerated ACE-inhibitors or CCB should be used. Hypothyroidism is a typical low-renin form of HT showing a better antihypertensive response to CCB and diuretics; in hypothyroidism a low-sodium
diet seems further to improve BP control. However, randomized clinical trials are needed to compare the efficacy on BP control of the different antihypertensive drugs in thyroid disorders.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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