

Hyperthyroidism and cardiovascular complications: a narrative review on the basis of pathophysiology

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Abstract

Cardiovascular complications are important in hyperthyroidism because of their high frequency in clinical presentation and increased mortality and morbidity risk. The cause of hyperthyroidism, factors related to the patient, and the genetic basis for complications are associated with risk and the basic underlying mechanisms are important for treatment and management of the disease. Besides cellular effects, hyperthyroidism also causes hemodynamic changes, such as increased preload and contractility and decreased systemic vascular resistance causes increased cardiac output. Besides tachyarrhythmias, impaired systolic ventricular dysfunction and diastolic dysfunction may cause thyrotoxic cardiomyopathy in a small percentage of the patients, as another high mortality complication. Although the medical literature has some conflicting data about benefits of treatment of subclinical hyperthyroidism, even high-normal thyroid function may cause cardiovascular problems and it should be treated. This review summarizes the cardiovascular consequences of hyperthyroidism with underlying mechanisms.

Key words: hyperthyroidism, subclinical hyperthyroidism, overt hyperthyroidism, atrial fibrillation, Graves' disease, toxic nodular goitre.

Introduction

Thyroid hormones have significant effects on the heart and cardiovascular system through many direct and indirect mechanisms. Since the first descriptions of hyperthyroidism and thyrotoxicosis, the cardiovascular symptoms have been alarming signs for the physician in the clinical presentation of the patient. Palpitations, exercise intolerance, dyspnoea, angina-like chest pain, peripheral oedema and congestive heart failure are common symptoms of hyperthyroidism [1, 2] that could show cardiovascular involvement of this relatively frequent endocrinological disorder. Although effects of iodization and world-wide use of radiocontrast agents may change the incidence, overt hyperthyroidism is common and affects 2–5% of the population [3, 4]. In hyperthyroid patients mortality is increased by 20% and the major causes of death are cardiac problems [5]. In the systematic review of Völzke *et al.*, eight studies suggesting a relationship between mortality and hyperthyroidism were evaluated and the relationship was not sufficient for clinical suggestions, except elderly

patients with subclinical hyperthyroidism [6]. But the association between subclinical hyperthyroidism and mortality in young and middle-aged people remains controversial in the medical literature [7]. Atrial fibrillation, which occurs in an estimated 10–25% of all overtly hyperthyroid patients, is the most common and worrying complication of hyperthyroidism [8]. This susceptibility to arrhythmic effects of thyroid hormones may have a genetic basis and recently the studies on molecular details of cardiac actions of thyroid hormones revealed some important knowledge [9]. Meanwhile the cause of hyperthyroidism may also change the cardiovascular risk; patients with toxic multinodular goitre have higher cardiovascular risk than patients with Graves' disease, probably because of older age, and patients with Graves' disease may have autoimmune complications, such as valvular involvement, cardiomyopathy and pulmonary arterial hypertension [10].

In this context, the aim of this narrative review is to summarize and organize the available evidence on the cardiac and hemodynamic effects of the thyroid hormones together with the cardiovascular complications of hyperthyroidism.

Molecular and cellular mechanisms of thyroid hormone effects on the heart

In recent years there has been significant progress to elucidate the molecular mechanisms of cardiac and hemodynamic complications of hyperthyroidism (Table I).

Triiodothyronine (T3) is an active thyroid hormone and it has genetic and cellular effects (on plasma membrane, mitochondria and sarcoplasmic reticulum) on cardiac muscle and blood vessels. Both T3 and T4 are lipophilic and they pass through the cellular membranes and the conversion of T4 to T3 occurs in many cells. T3 acts on THR_s (thyroid hormone receptors) in the nucleus, creating dimers of 9-cis-retinoic acid receptor (RXR) [11]: the formed complexes recognize some specific DNA consensus sequences, the thyroid response elements (TREs), located in the enhanced region of the genes to initiate the transcription [12].

In myocytes, thyroid hormones act on many TREs, such as alpha myosin heavy chain fusion (MHC- α), sarcoplasmic reticulum calcium-activated ATPase (SERCA), the cellular membrane Na-K pump (Na-K ATPase), β 1 adrenergic receptor, cardiac troponin I, and atrial natriuretic peptide (ANP) [13–15], and some genes are also suppressed, such as β -myosin heavy chain fusion (MHC- β), adenylyl cyclase (IV and V) and the Na-Ca antiporter [16].

Thyroid hormone upregulates α , but downregulates β -chain in myocytes [17]. The final effect of thyroid hormones in animal studies is increased rate of V1 isoform of MHC (MHC α/α) synthesis that is characteristically faster in myocardial fibre short-

ening [16, 18]. A similar effect has also been observed in preliminary human studies [19, 20].

Thyroid hormones also have effects on SERCA, which is responsible for the rate of calcium uptake during diastole, by actions on calcium activated ATPase and its inhibitory cofactor phospholamban [21, 22]. Thyroid hormones enhance myocardial relaxation by upregulating expression of SERCA, and downregulating expression of phospholamban. The greater reduction in cytoplasmic calcium concentration at the end of the diastole increases the magnitude of systolic transient of calcium and augments its capacity for activation of actin-myosin subunits. As confirmation, phospholamban deficient mice showed no increase in heart rate after thyroid hormone treatment [23].

On the plasma membranes, T3 exerts direct extragenic actions on the functions of other ion channels such as Na/K ATPase, Na/Ca⁺⁺ exchanger, and some voltage gated K channels (Kv 1.5, Kv 4.2, Kv 4.3) affecting myocardial and vascular functions [24, 25] coordinating electrochemical and mechanical responses of myocardium [26, 27]. It prolongs the activation of Na channels in myocardial cells [28] and induces intracellular Na uptake and secondary activation of the Na-Ca antiporter, which can partly explain the positive inotropic effect. T3 exerts a direct effect on L-type calcium channels, resulting in abbreviation of action potential duration [29, 30].

The strong inotropic activity of thyroid hormones is probably due to an increased number of β -adrenergic receptors [31]. Circulating catecholamine levels are in fact the same, but G protein and β -receptors increase [32]. The sensitivity of the cardiovascular system to adrenergic stimulation is not changed by thyroid hormones [33, 34]. The changes in the heart rate result from both an increase in sympathetic tone and decrease in parasympathetic tone [35, 36].

These genomic effects fail to explain fast actions of thyroid hormones on the cardiovascular system. Non-genomic effects promote rapid changes, such as increased cardiac output [37–39]. The hemodynamic consequences of hyperthyroidism and non-genomic changes for plasma membranes occur acutely and contribute to these rapid changes. Studies indicate that thyroid hormone activates acute phosphorylation of phospholamban, and that also partly explains the homology between thyroid hormone and the adrenergic system effects on the heart [35].

In an experimental study on rats, thyroid hormones upregulated connexin-40, a gap junction protein of myocardium important for the transport of electrical activity, and this may be one of the pathogenetic mechanisms of atrial fibrillation in hyperthyroidism [40]. In another animal study the

Table I. Cardiovascular system-related cellular actions of thyroid hormones

Cell	Cellular target	Action	Biological and biochemical effect	Clinical effect	References
Cardiac myocytes	MHC- α	Upregulation	Increased V1 isoform	Faster myocardial fibre shortening	[3, 6, 8]
	MHC- β	Downregulation	Decreased slower fibres		
	SERCA	Upregulation	Greater reduction in cytoplasmic calcium concentration	Increased systolic calcium transient and ability to activate muscle fibres	[11–13]
	Phospholamban	Downregulation	at the end of the diastole		
	Cardiac troponin I	Increased expression	Increased synthesis of troponin I in myocytes	More efficient contraction	[5]
	Connexin-40	Upregulation	Increased conduction from atrium to myocytes and between myocytes	Improved atrial connection to fibres	[30]
Myocardial and vascular smooth muscle cells	Na-K ATPase	Increased expression of the α - and β -subunits	Increased intracellular K^+ especially in ventricular myocytes	Tendency to hypokalaemic thyrotoxic paralysis	[14, 15, 19, 20]
	Voltage-gated K channels	Increased expression of Kv1.5, Kv2.1, Kv4.2, Kv4.3	Delayed rectifier K^+ currents	Changes in action potential duration	
	Ca ²⁺ channels	Inhibition of atrial L-type calcium channel expression	Affects calcium influx	Shorter action potential duration	
Vascular smooth muscle cells	K ⁺ channels	Increased K ⁺ channel activity	Affects contractility	Vasodilatation, decreased PVR	[44]
Juxtaglomerular cells	β 1 adrenergic receptors	Secondary activation of renin synthesis due to peripheral vasodilatation	Na retention and increased blood volume	Increased heart rate, decreased diastolic BP, wider pulse pressure	[45]

authors suggested that the connexin-43 phosphorylation was downregulated by T3 in diabetic rats and decreased adaptation of the heart to hyperglycaemia and this may render the heart prone to ventricular arrhythmias [41]. In fact, thyroid hormone receptor α 1 is predominantly expressed in cardiac myocardium and may have an important role in cardiac myoblast differentiation by an ERK kinase dependent process, but its clinical relevance is not known [42]. Also the extracellular signal-regulated kinase (ERK) pathway may have a role in negative cardiac remodelling and decreased cardiac contractile function in hyperthyroidism, by inhibition of the Raf-1/ERK pathway by T3 [43, 44].

Administration of a β -adrenergic receptor antagonist to patients with hyperthyroidism slows the heart rate, but does not alter systolic or diastolic contractile performance [45, 46], confirming that thyroid hormone acts directly on cardiac muscle [16, 21, 47]. Meanwhile, thyroid hormone may have

direct (without autonomous nervous system) effects on the sinoatrial node [48, 49] and oxidative stress in animal studies [50]. The heart rate increases due to increased sinoatrial activity, lower threshold for atrial activity, and shortened atrial repolarisation [51, 52]. Together with hemodynamic changes, i.e. volume preload increases due to activation of the renin-angiotensin system [53], contractility increases due to increased metabolic demand and the direct effect of the thyroid hormone on heart muscle [54], and systemic vascular resistance decreases because of triiodothyronine-induced peripheral vasodilatation [55], the result is a dramatic increase in cardiac output [56].

Local type 2 iodothyronine deiodinase up-regulation may also be involved in cardiac remodelling via activation of thyroid hormone signalling pathways involving Akt and p38 mitogen-activated protein kinase (MAPK) in thyrotoxic-dilated cardiomyopathy [57]. Preclinical studies in which Akt was

blocked by an angiotensin-II type 2 receptor blocker showed that this blockage might prevent thyroxine-mediated cardiac hypertrophy [58]. Meanwhile, hypertrophied myocytes may be susceptible to apoptotic stimulation by angiotensin II in hyperthyroidism [59].

All this knowledge could drive the clinician to a more correct treatment choice of hyperthyroidism-related cardiovascular diseases.

Hemodynamic effects of thyroid hormones

Beyond what is reported above, hemodynamic effects of thyroid hormones are generally non-genomic and faster, by direct effects on heart and blood vessels. In the peripheral vascular system, the rapid use of oxygen, increased production of metabolic end products and relaxation of arterial smooth muscle fibres by thyroid hormone cause peripheral vasodilatation [24]. This fall in peripheral vascular resistance (PVR) plays the central role in all hemodynamic changes caused by thyroid hormones [60]. Decreased PVR causes an increase in heart rate, a selective increase in blood flow of some organs (skin, skeletal muscles, heart), and a fall in diastolic pressure with consequent widening of pulse pressure. Vasodilatation without an increase in renal blood flow causes a reduction in renal perfusion and activation of the renin-angiotensin system that causes sodium retention and increased blood volume [61]. In addition, thyroid hormones regulate erythropoietin secretion and increased red cell mass may also contribute to the blood volume increase [62]. Improved diastolic relaxation and increased blood volume increased left ventricular end-dias-

tolic volume (LVEDV). Reduced PVR and increased LVEDV means increased preload and decreased afterload; thus the stroke volume increases. Increased stroke volume and increased heart rate lead to doubling or tripling of cardiac output, which cannot be solely explained by an increased metabolic rate of the body [63] (Figure 1).

The importance of the contribution of decreased systemic vascular resistance to the increase in systemic blood flow in patients with hyperthyroidism is evidenced by studies in which the administration of arterial vasoconstrictors, atropine and phenylephrine, decreased peripheral blood flow and cardiac output by 34% in patients with hyperthyroidism but not in normal subjects [64, 65].

Overt hyperthyroidism

Palpitations resulting from an increase in the rate and strength of cardiac contractility are present in the majority of patients, independently from the cause of hyperthyroidism [35]. In overt hyperthyroidism, ambulatory 24-h electrocardiogram monitoring demonstrates that heart rate is constantly increased during the day and exaggerated in response to exercise, and diurnal rhythm is usually unchanged [66].

The most common ECG abnormality is sinus tachycardia and shortened PR interval, and frequently intra-atrial conduction is prolonged, which is observed as an increase in P wave duration. Intra-ventricular conduction delay in the form of right bundle branch block is present in around 15% of patients, and atrioventricular block may also occur due to unknown reasons. Increased dispersion of

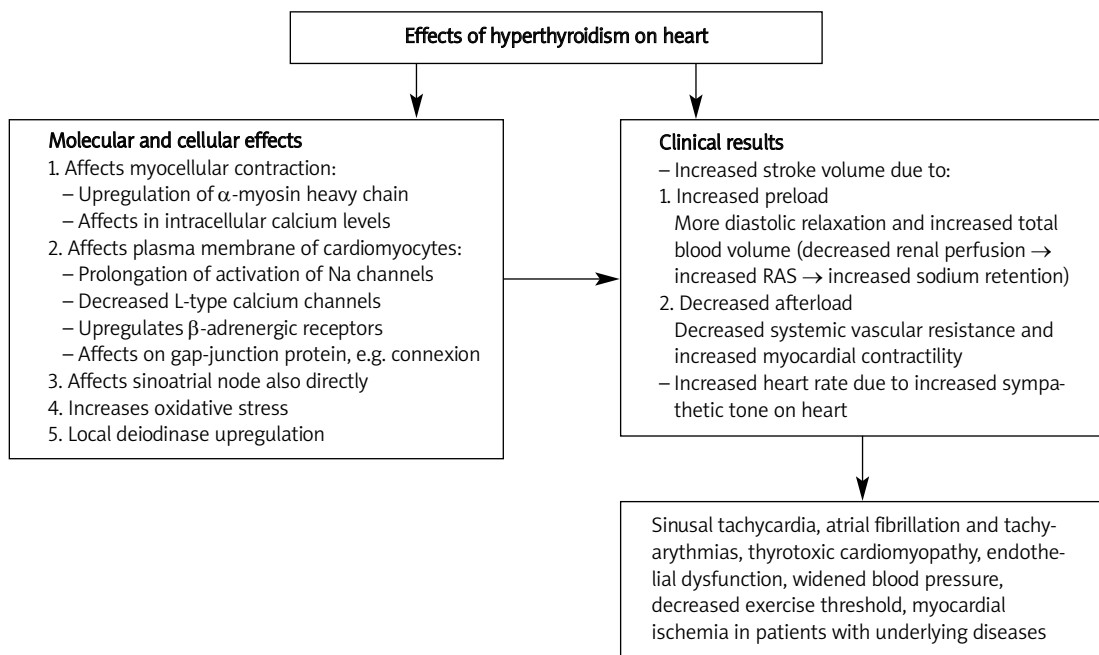


Figure 1. Summary of molecular and clinical effects of hyperthyroidism on cardiovascular system

QT interval corrected by the heart rate (QTcD) and pulmonary hypertension may also be observed, but their mechanisms are not clear; the same cardiac and hemodynamic changes together with autoimmunity in Graves' patients may have a role [67, 68]. Hyperthyroidism is associated with shortened action potential and increased expression of L-type calcium channel 1D, enhances Na and K permeability, and affects Na pump density [69].

The forced increase in preload and total blood volume increases cardiac work, and myocardial hypertrophy is commonly seen [70].

The most common rhythm disturbance in hyperthyroid patients is sinus tachycardia [35]. Its clinical impact however is overshadowed by that of patients with atrial fibrillation. The prevalence of atrial fibrillation (AF) and less common forms of supraventricular tachycardia in this disease ranges from 2% to 20% [71, 72]. When compared with the prevalence of atrial fibrillation of 2.3% in a control population with normal thyroid function, the prevalence of atrial fibrillation in overt hyperthyroidism was 13.8%, peaking at up to 15% in patients older than 70 years of age [69]. Atrial fibrillation is generally accompanied by a rapid ventricular response. It is more common in men and its significance increases with age, after 40 years [72].

The majority of patients with hyperthyroidism and AF have an enlarged left atrium when compared to hyperthyroid people with sinus rhythm [73]. As in the case of angina or heart failure, the development of AF should not be attributed only to hyperthyroidism, and the underlying organic heart diseases should be investigated.

Atrial fibrillation usually reverts to sinus rhythm by achievement of a euthyroid state, if the patient is younger and the duration of hyperthyroidism is not long. β -Adrenergic blockade may be effective to control the ventricular rate. Increased plasma clearance of β -blockers may necessitate higher doses [74]. Among them propranolol has the advantage of blocking the conversion of T4 to T3 in peripheral tissues, but other cardioselective β -blockers have a longer half-life and are equally effective on the heart. In cardiac arrhythmias intravenous infusion of calcium blockers should be avoided due to the risk of a further fall in PVR [75]. It is still controversial whether the patients with AF should have anticoagulant therapy to prevent systemic embolization. It is advised to evaluate each patient on a case-by-case basis, and determine the risk of bleeding over embolization [76, 77]. In younger patients with hyperthyroidism and AF who do not have other heart disease, hypertension, or independent risk factors for embolization, the risk of anticoagulant therapy may suppress its benefits. But it would be appropriate to administer anticoagulant agents to older patients with known or sus-

pected heart diseases or AF with longer duration. When oral anticoagulants are used, it should be considered that hyperthyroid patients will need smaller doses than euthyroid ones, due to faster elimination of vitamin-K dependent clotting factors [78].

In the patients with AF the maintenance of sinus rhythm is not possible until the euthyroid state is restored, so electrical cardioversion is not recommended without euthyroid status.

Many hyperthyroid patients experience exercise intolerance and exertional dyspnoea, in part because of weakness in the skeletal and respiratory muscle [79] and also due to inability to increase heart rate or lower vascular resistance further, as normally occurs in exercise [80]. The term "high output heart failure" has not been used in the last decades, because it is clear that the heart is still able to increase cardiac output at rest and with exercise. In the setting of low vascular resistance and decreased preload, cardiac functional reserve is compromised and cannot rise further to accommodate the demands of submaximal or maximal exercise [81]. About 6% of thyrotoxic patients develop heart failure and less than 1% develop dilated cardiomyopathy with impaired left ventricular systolic dysfunction, due to a tachycardia-mediated mechanism leading to an increased level of cytosolic calcium during diastole with reduced contractility of the ventricle and diastolic dysfunction, often with tricuspid regurgitation [82]. In the recent study of Yue *et al.*, diastolic dysfunction was more prominent in thyrotoxic patients older than 40 years of age, whereas in younger ones a marked reduction in peripheral vascular resistance and increased cardiac output were prominent [83].

Hyperthyroidism may complicate or cause pre-existing cardiac disease because of increased myocardial oxygen demand and increased contractility and heart rate, and may cause silent coronary artery disease, anginas or compensated heart failure and even endothelial dysfunction [84]. Treatment of heart failure with tachycardia should include a β -blocker, considering its contraindications in each patient. Furosemide may help to reverse the volume overload and digoxin is less beneficial when compared with euthyroid heart failure patients, because there may be relative resistance to its action, due to greater blood volume (distribution) and the need to block more Na-K-ATPase in the myocardium [78].

Subclinical hyperthyroidism

Subclinical hyperthyroidism is a state characterised by low serum thyrotropin levels and normal serum thyroid hormone concentrations. Over the past decades this state has also been found to be associated with some abnormalities in cardiac function. Enhanced systolic function and impaired dias-

tolic function due to slowed myocardial relaxation may cause increased left ventricular mass in these subjects, together with increased heart rate and arrhythmias, by similar mechanisms as overt hyperthyroidism [85–87]. In people over 60 years of age subclinical hyperthyroidism is associated with tripled risk of atrial fibrillation during a 10-year follow-up period [88]. In a recent cross-sectional study with 29 patients, subclinical hyperthyroidism was found to be related to impaired functional response to exercise with low oxygen consumption and exercise threshold, together with slower heart rate recovery [89]. Patients with subclinical hyperthyroidism show higher QT dispersion and lower heart rate variability, which means impaired sympatho-vagal balance, increased sympathetic tone in the presence of decreased vagal tone and increased inhomogeneity of ventricular recovery times [90]. Besides antithyroid treatment strategies β -blocker therapy reduces heart rate and improves left ventricular mass, but positive inotropic response persists [46]. Subclinical hyperthyroidism is associated with increased cardiovascular mortality [91]. In the study of Heeringa *et al.* with 1426 patients, it was found that even high-normal thyroid function may increase the risk of AF [92]. Besides increased AF and thromboembolic events, increased left ventricular mass and left ventricular function may be the reason. Thus, it is advised to measure serum thyrotropin in all elderly patients with systolic hypertension, widened blood pressure, recent-onset angina, atrial fibrillation and any exacerbation of ischemic heart disease, and treat [80, 93].

Conclusions

Hyperthyroidism is a common thyroid problem which has many effects on almost all organ systems in the body, including bone metabolism, dermatological effects, the gastrointestinal system and the cardiovascular system. Cardiovascular effects are the most common and dangerous effects, and generally they cause the main complaints leading the patient to come to hospital. Cardiovascular actions of thyroid hormones are presented via different mechanisms in the body, including complex and multisystemic interactions. Knowing the details of these mechanisms may provide us with some valuable clues during the treatment of the patients.

Although the most common cause of hyperthyroidism is Graves' disease [94], toxic multinodular thyroid disease is also common, especially in iodine deficient or newly iodinated areas of the world. Meanwhile the patients may be using some medications that may interfere with thyroid functions, such as amiodarone [95] and radiocontrast agents [96] and drugs with fewer side effects and perhaps those without an iodine moiety (such as drone-

darone) could be evaluated for arrhythmia treatment [97]. Treatment of hyperthyroidism is important to prevent arrhythmic complications and even a subclinical hyperthyroid state should be treated, especially in high-risk patients. Another important point is prevention of iatrogenic hypothyroidism during treatment, because hypothyroidism also brings some other cardiovascular and general risks [98–100].

In conclusion, thyroid hormones exhibit their cardiovascular effects through different mechanisms and both hyperthyroidism and hypothyroidism have negative effects on the cardiovascular system. In hyperthyroid patients the euthyroid state should be established carefully, and by evaluating each patient with accompanying risks, cause of hyperthyroidism, patient characteristics, comorbidities, and his/her current medications.

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