Hernando and Eliana, Endocrinol Metab Synd 2015, 4:2
DOI: 10.4172/2161-1017.1000166

Endocrinology & Metabolic Syndrome

Review Article Open Access

Role of Thyroid Hormones in Different Aspects of Cardiovascular System

Vargas U Hernando* and Morales S Eliana

Division of Endocrinology and Metabolism, Internal Medicine Department, University of Cauca, Popayán-Cauca, Colombia

Abstract

Besides its metabolic and thermoregulatory tissue effects, thyroid hormones plays a fundamental role in the cardiovascular homeostasis, mediated by genomic and non-genomic effects. Consequently, thyroid hormones deficits, as well as excesses, are expected to result in profound changes in cardiac function regulation and cardiovascular hemodynamics. Hyperthyroidism induces a hyperdynamic cardiovascular state, which is associated with enhanced left ventricular systolic, diastolic function, and the chronotropic and inotropic properties of thyroid hormones. On the other hand; in a hypothyroid state, thyroid hormones deficiency results in lower heart rate and weakening of myocardial contraction and relaxation, with prolonged systolic and early diastolic times. Subclinical hypothyroidism is characterized by abnormal lipid metabolism and cardiac dysfunction; diastolic hypertension conferring an elevated risk of atherosclerosis, and ischemic heart disease. The risk of cardiovascular mortality and atrial fibrillation [but not other outcomes] in subclinical hyperthyroidism is higher among patients with very low levels of thyrotropin. Finally, medications such as amiodarone may induce hypothyroidism [mediated by the Wolff-Chaikoff] as well as hyperthyroidism [mediated by the Jod-Basedow effect]. In both instances, the underlying cause is the high concentration of iodine in this medication.

Keywords: Thyroid; Receptor; Deiodinases; Hyperthyroidism; Tachycardia; Cardiovascular; Hypothyroidism; Subclinical dysfunction; Heart, Genomic, Non-genomics, Atrial fibrillation; Amiodarone; Mortality

Abbreviations: ADMA: Asymmetric Dimethyl Arginine; AMI: Acute Myocardial Infarction; AIH: Amiodarone-Induced Hypothyroidism; AIT: Amiodarone-Induced Thyrotoxicosis; AF: Atrial Fibrillation; ANP: Atrial Natriuretic Peptide; AV: AtrioVentricular; BP: Blood Pressure; CHD: Coronary Heart Disease; CK-MB: Creatinine Kinase-M; DCM: Dilated Cardiomyopathy; T2: Diiodothyronine; DDAH: Dimethylarginine Dimethylaminohydrolase; ECG: Electrocardiogram ; FT_3: Free T_3; GPCR: G Protein-Coupled Receptor; HPT: Hypothalamic/Pituitary/Thyroid Axis; 1-Arg: l-Arginine; LTS: Low T3 Syndrome; LV: Left Ventricular; LVEF%: Left Ventricular Ejection Fraction; MACEs: Adverse Major Cardiac Events; MAPK: Mitogen-Activated Protein Kinase; NADH: Nicotinamide Adenine Dinucleotide; NOX: NADH Phosphate Oxidase; NO: Nitric Oxide; ACor1: Nuclear Co-repressor 1; PPARs: Peroxisome Proliferator-Activated Receptors; PI3K: Phosphatidylinositol-3-Kinase; PLB: Phospholamban; PLC: Phospholipase C; PLD: Phospholipase D; PKA: Protein Kinase A; PKC: Protein Kinase C; ROS: Reactive Oxygen Species; RAR: Retinoic Acid Receptor; RAAS: Renin-Angiotensin-Aldosterone system; RXR: Retinoid X Receptor; rT_3: reverse T_3; SERCA: Sarcoplasmic Reticulum Ca_2^+-ATPase; SMRT: Silencing Mediator of Retinoic Acid; SRC: p160/Steroid Receptor Co-activator; STATs: Signal Transducer and Activators of Transcription; STEMI: ST-Elevation Myocardial Infarction; SHyper: Subclinical Hyperthyroidism; SHypo: Subclinical Hypothyroidism; SCTD: Subclinical Thyroid Dysfunction; TMC: Tachycardia-Mediated Cardiomyopathy; TRs: Thyroid Hormone Receptors; TREs: Thyroid Hormone Response Elements; TH: Thyroid Hormones; TSH: Thyroid Stimulating Hormone; TRH: Thyrotropin-Releasing Hormone; T_4: Thyroxine; TAAR1: Trace Amine-Associated Receptor 1; T_3: Triiodothyronine

Introduction

Thyroid Hormones [TH] play critical roles in differentiation, growth, and metabolism; they act as pleiotropic factors in many tissues during development, by regulating genes involved in differentiation. TH has important tissue effects, which are classified into three major aspects: general thermogenesis, mediated by increase the basal metabolic rate; general metabolic effects, mediated by stimulates protein and lipid turnover, and carbohydrate metabolism; and effects on growth and developmental. Peripheral metabolism of TH is a critical component of the impact these hormones have on intracellular function. TH action is mediated by multiple Thyroid Hormone Receptor isoforms [TRs] derived from two distinct genes. TRs are intracellular DNA-binding proteins that function as hormone-responsive transcription factors; they can activate or repress gene transcription depending on the promoter context and ligand-binding status. Transport of TH across the plasma membrane does not take place by passive diffusion, but involves specific transporters - TH enters cells through transmembrane transporter - once inside the nucleus, the hormone binds to its receptor, and the hormone-receptor complex interacts with specific DNA sequences in the promoter regions of responsive genes; changes in gene expression caused by TH have a significant effect on the contractile apparatus and the sarcoplasmic reticulum. TRs mediate the biological activities of T3 via transcriptional regulation, and the genes that are transcriptionally regulated by T3 are critical in the regulation of systolic and diastolic properties of the myocardium. T3 is the biologically active TH; it is mostly generated peripherally by 5'-monodeiodination of T4. T4 has little biological activity by itself and is considered a prohormone, as activation occurs through outer ring deiodination to T3.

Increased or reduced action of TH on certain molecular pathways in the heart and vasculature causes relevant cardiovascular derangements; in presence of hyperthyroidism, the preload is increased; there is high cardiac output, with increased heart rate, reduced peripheral vascular resistance and hyperdynamic circulation. The reduction in systemic vascular resistance is responsible for the decrease in renal perfusion pressure and for activation of the Renin-Angiotensin-Aldosterone

***Corresponding author:** Vargas U Hernando, Division of Endocrinology and Metabolism, University of Cauca Popayán-Cauca, Hospital Universitario San José, Carrera 6 No 10N-142 3er piso, Colombia, USA, Tel: 8234508; Fax: 8234712; E-mail: hernandovargasu10@yahoo.com

Received February 03, 2015; **Accepted** March 13, 2015; **Published** March 23, 2015

Citation: Hernando VU, Eliana MS (2015) Role of Thyroid Hormones in Different Aspects of Cardiovascular System. Endocrinol Metab Synd 4: 166. doi:10.4172/2161-1017.1000166

System [RAAS], with the resulting increase in sodium absorption and blood volume. The increased risk of cardiac mortality could be a consequence of the increased risk of arrhythmias, especially Atrial Fibrillation [AF], and for the presence of heart failure. In presence of hypothyroidism, there are important changes in cardiac structure and function, this state is characterized by low cardiac output, decreased heart rate and stroke volume, and reduction in systolic and diastolic functions; there is also a decline in cardiac preload and blood volume, as well as a drop in renal perfusion with impaired free water clearance and hyponatremia. An increase in cardiovascular risk and mortality has also been described.

What is Already Known on this Topic

1. Coronary Heart Disease [CHD] is the leading cause of death with 17 million deaths worldwide from a total of 57 million annually.
2. The burden of cardiovascular disease is expected to markedly increase because of the global aging of the population and increasing exposure to detrimental lifestyle-related risk in low and middle income countries.
3. Because unhealthful diet, tobacco use, and decreased physical activity levels are among the major drivers of the CHD, prevention through promoting healthful diet and lifestyle should remain one of the cornerstones of global cardiovascular disease reduction efforts.
4. Thyroid disorders are amongst the most prevalent of medical conditions.
5. The thyroid and the cardiovascular system are closely related, the adverse consequences on the heart of overt thyroid disease are well-known and even subclinical forms of both hyperthyroidism and hypothyroidism are associated with fatal outcomes.

De-iodinases, the Balance and Control of TH

TH synthesis and secretion is tightly regulated by a negative-feedback system that involves the hypothalamus, pituitary, and thyroid gland -Hypothalamic/Pituitary/Thyroid [HPT] axis- The control of thyroid function is mediated by pituitary thyrotropin [Thyroid Stimulating Hormone - TSH] and the control of TSH secretion is, in turn, influenced by Thyrotropin Releasing Hormone [TRH] of hypothalamic origin [is synthesized in the paraventricular nucleus of the hypothalamus]. TRH binds to its receptors in pituitary thyrotropes, a subpopulation of pituitary cells that secrete TSH. Thyrotropin regulates iodide uptake mediated by the sodium/iodide symporter, followed by a series of steps necessary for normal TH synthesis and secretion. The set point for TH production and secretion by the thyroid gland is regulated by the TRH, determining the equilibrium between serum TSH and TH concentrations [1,2]. The major form of TH produced by the thyroid is the prohormone Thyroxine [T4] which can be converted into the biologically active Tri-iodothyronine [T3] mediated by the removal of an iodide by deiodinases [deiodinases constitute a group of thioredoxin fold-containing selenoenzymes that play an important function in homeostasis, control and actions of TH, and selectively remove iodide from thyroxine and its derivatives, thus activating or inactivating these hormones which have a tissue-specific distribution]. Deiodinases exert a major metabolic control of intracellular TH concentrations leading to a tissue-specific TH bioavailability. All deiodinases are membrane-anchored proteins of 29-33 kDa that share substantial sequence homology; they catalyze and sequentially remove stereo-specific iodine atoms from T4, generating active and inactive isomers of both T3 and diiodothyronine [T2]. The deiodination of T4, T3, and other iodothyronines is an integral component of TH homeostasis [3,4]. There are three deiodinases: *Type 1* [D1], localized to the plasma membrane and expressed in liver, thyroid and kidney, it catalyzes removal of inner or outer ring iodine atoms in equimolar proportions to generate T3, reverse T3 [rT3], or T2, depending on the substrate. Most of the circulating T3 is derived from conversion of T4 to T3 by the actions of D1. *Type 2* [D2], which is considerably more efficient than D1, catalyzes only the removal of an outer ring iodine atom from T4, generating the active product T3. D2 is considered the main T4-activating enzyme, given its high substrate affinity. D2-mediated T3 production happens intracellularly; subsequently, T3 exists the cells and enters the plasma compartment, being responsible for 70% of all extra-thyroidal T3 production in healthy humans. The major role of D2 is to control the intracellular T3 concentration, its availability to the nucleus, and the saturation of the nuclear T3 receptor in target tissues; it is mainly active in brain, pituitary, and skeletal muscle. And *Type 3* [D3], which is expressed in the brain and other tissues; it irreversibly inactivates T3, or prevents activation of T4 by catalyzing removal of an inner ring iodine atom to generate T2 or rT3, respectively. D3 is an integral membrane protein that exerts its role as a homodimer. It is recycled through a system of endosomal clathrin-coated vesicles, this might suggest a possible mechanism for D3 reactivation, and furthermore the possibility that this enzyme acts on both extracellular and intracellular pools of T3 and T4. Moreover, the inactivation of D3 prevents TH access to specific tissues at critical times and reduces TRs saturation (Figure 1). Given these functions, D3 is considered the major physiological inactivator and terminator of TH action at the peripheral level [5,6].

Genomic and Non-genomic Effects of TH

The molecular mechanisms of actions of TH are genomic and non-genomic. Both the non-genomic and genomic effects of T3 act in concert to regulate cardiac function and cardiovascular hemodynamics; the genomic mechanism involves a primary interaction of T3 with TRs, and the formation of intranuclear complexes of well-described co-activators or co-repressors that, via binding to the promoter regions of TH-responsive genes, modulate transcription. Non-genomic

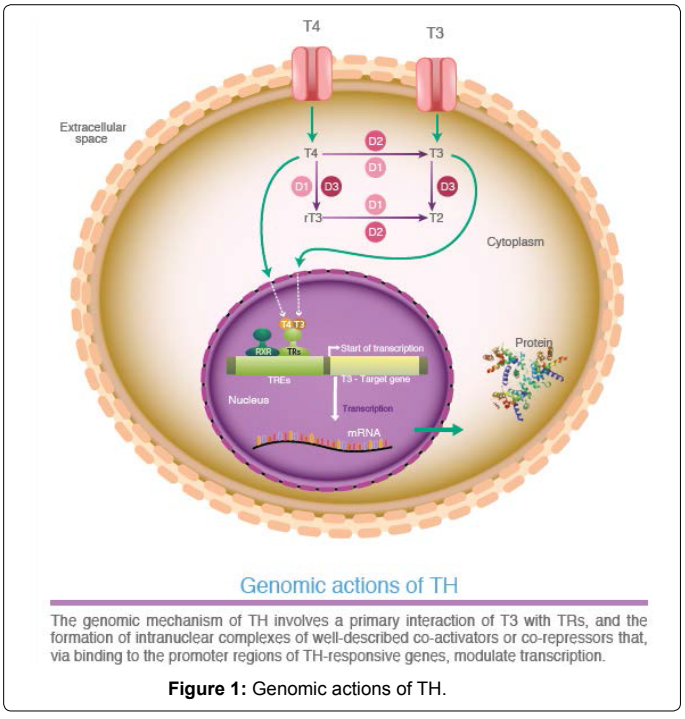


Figure 1: Genomic actions of TH.

mechanisms of TH may be initiated at the plasma membrane, in cytoplasm or at intracellular organelles, such as mitochondria. TH signaling is a local phenomenon, with target cells playing a major role through restricted expression of the activating or inactivating deiodinases. This local role played by the deiodinases in customizing TH signaling is the main way in which TH exerts its metabolic effects. Although the thyroid gland produces predominantly T4, the primary biologically active form of the hormone is T3, which binds to, and activates, the TRs. The TRs belong to the nuclear receptor superfamily that includes the estrogen receptor, vitamin D receptor, Peroxisome Proliferator-Activated Receptors [PPARs], Retinoic Acid Receptor [RAR] and Retinoid X Receptor [RXR]. TRs homodimerize or interact with other nuclear receptors and control essential functions in growth, development and metabolism, and are important for normal functioning of almost all tissues. TRs are transcription factors that bind to TH Response Elements [TREs] in the regulatory regions of target genes (Figure 1). TRs are encoded by two genes, THRA and THRB, located on chromosomes 17 and 3, respectively; T3 exerts many of its actions through its TRs: TRα1, TRα2, TRβ1, and TRβ2. TRs, with the exception of TRβ2, are expressed in all tissues and the pattern of expression varies in different types of tissues. TRα1 is predominantly expressed in the myocardium and regulates important genes related to cell differentiation and growth, contractile function, pacemaker activity, and conduction. The three major TRs isoforms, TRα1, TRβ1, and TRβ2, are expressed in a tissue-specific fashion and regulate a spectrum of metabolic and developmental functions [7,8].

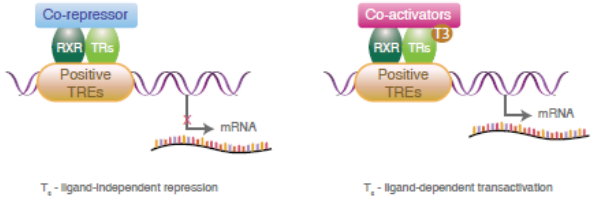
Like other nuclear receptors, TRs bind TREs comprised of degenerate repeats of the sequence AGGTCA, usually as heterodimers with RXR. From these locations, the TRs recruit co-regulator complexes that influence gene expression, and T3 modulates transcription by inducing conformational changes in the receptor C-terminal ligand binding domain which, in turn, alters the complement of TRs associated co-regulators. Co-regulators interact with nuclear receptors and other transcription factors to alter chromatin and stimulate [co-activators] or repress [co-repressors] gene expression. In the absence of the T3 ligand, TRs can repress the expression of genes leading to gene silencing. The selective actions of TRs are influenced by local ligand availability, by transport of TH into the cell by related transporters, by the relative expression and distribution of the TRs isoforms and nuclear receptor co-repressors and co-activators; and, finally, by the sequence, arrangement, and promoter context of the TREs. TH binds to serum transport proteins that help ensure even delivery of hormone to all tissues, cell type-specific membrane transporters, cytoplasmic interacting proteins, enzymes that variously activate pro-hormones or inactivate active hormones, and the TRs themselves [9].

Classically, on positively regulated TH targets, the presence of T3 allows the binding of co-activators, such as the p160/Steroid Receptor Co-activator [SRC] family comprises three pleiotropic co-regulators [SRC-1, SRC-2, and SRC-3; otherwise known as NCOA1, NCOA2, and NCOA3, respectively]. Such pleiotropy is achieved through their inherent structural complexity, which allows this co-regulator class to control both nuclear receptor and non-nuclear receptor signaling.

These co-activators then recruit machinery to allow the activation of gene expression. In the absence of ligand, co-repressors, such as Nuclear Co-repressor 1 [NCoR1] or Silencing Mediator of Retinoic Acid [SMRT or NCoR2] bind and recruit complexes to repress transcription. The processes by which negative TH targets are repressed or transcribed are not well understood, but active T3 repression does require SRC-1.

In summary, the classical genomic actions of T3 are mediated by high-affinity nuclear receptors that regulate gene expression directly; this process begins with the entry of T3 into the cardiomyocyte, through specific transport proteins located within the cell membrane; once in the cardiomyocyte, T3 enters the nucleus and interacts with specific transcriptional co-activators or with co-repressors. Occupancy of these receptors by T3, in combination with recruited co-factors, allows the TR complex to bind or release specific DNA sequences. Characteristics of the genomic actions of TH include the requirement for access of the hormone to the cell interior, translocation of the hormone to the nucleus, altered rates of gene transcription, generation of specific mRNAs, translation and changes in cell content, or secretion of specific gene products. One or more hours are usually required for genomic mechanisms to be manifested. There is no widely accepted model for T3 action on negatively regulated target genes; but in the absence of T3, a positively regulated target gene will have a TREs to which the THR binds and recruits a co-repressor, the co-repressor forms a complex with histone deacetylases, which modify the chromatin structure resulting in a subsequent a decrease in gene transcription. In the presence of T3, the repressive complex is destabilized and the co-repressors are released, co-activators induce remodeling of chromatin by acetylating or methylating histones or altering the DNA conformation, which changes the interactions among RNA polymerase and other transcriptional factors (Figure 2) [10,11].

In contrast, the non-genomic effects of TH occur rapidly and are unaffected by transcription inhibitors and protein synthesis. As tissue levels of TH are relatively constant in the intact organism, the terms "acute" or "rapid onset" do not reflect TH-mediated physiologic action. So, it is more accurate to consider non-genomic mechanisms as those actions of TH that are not initiated by the binding of the hormone to the intranuclear TRs and that are unaffected by inhibitors of transcription and translation; therefore, these non-genomic actions of TH are extranuclear, independent of TRs, occur at posttranscriptional level and require a plasma membrane receptor or nuclear receptors located in cytoplasm. The plasma membrane receptor is located on integrin αVβ3 at the Arg-Gly-Asp recognition site important to the binding by the integrin of extracellular matrix proteins; T4 is bound with greater affinity at this site than T3. Mitogen-Activated Protein Kinase [MAPK; ERK1/2] transduces the hormone signal into complex cellular/nuclear events. A possible mediator of these effects is the Trace Amine-Associated Receptor 1 [TAAR1] which is a G Protein-Coupled Receptor [GPCR]. This TAAR1, binds to 3-iodothyronamine, which is an endogenous amine and a TH metabolite, is not a ligand for nuclear TRs, but stimulates with TAAR1. The downstream events involved in TAAR signaling are not fully understood, but it is likely that TAAR1 could couple with Gs protein, resulting in adenylate cyclase activation; the interaction among TAAR1 and iodothyronamine



In the absence of T3, a positively regulated target gene will have a TREs to which the THR binds and recruits a co-repressor, the co-repressor forms a complex with histone deacetylases, which modify the chromatin structure resulting in a subsequent a decrease in gene transcription. In the presence of T3, the repressive complex is destabilized and the co-repressors are released, co-activators induce remodeling of chromatin, which changes the interactions among RNA polymerase and other transcriptional factors.

Figure 2: A general model of T3 action.

can rapidly influence several physiological manifestations of TH action, including body temperature, heart rate, and cardiac output. MAPK-dependent TH actions include plasma membrane ion pump stimulation and specific nuclear events. These Non-genomic actions are also mediated by other signal transduction pathways that include among others the activation of Protein Kinase C [PKC], Protein Kinase A [PKA], Phosphatidylinositol-3-Kinase [PI3K], and the regulation of phospholipid metabolism by activation of Phospholipase C [PLC] and Phospholipase D [PLD].

The proposed mechanism by which TH activates the MAPK and Signal Transducer and Activators of Transcription [STATs] signaling pathways indicates that TH initially bind a putative GPCR; TH binding results in activation of PLC, PKC and PKA. PKC then activates PLD sustaining the non-genomic response and also activates the serine/threonine kinases Raf1 [Raf1 activation initiates a MAPK cascade that comprises a sequential phosphorylation of the dual-specific MAPK kinases [MAP2K1/MEK1 and MAP2K2/MEK2] and the extracellular signal-regulated kinases [MAPK3/ERK1 and MAPK1/ERK2]]. Tyrosine phosphorylation of MAPK results in its nuclear translocation and its phosphorylation of TRs, STATs and p53. Serine phosphorylation of TRs induces dissociation from the co-repressors NCoR1 and SMRT, and increases transcriptional activity following binding of ligand - RXR, co-activators p160/SRCs and TRAPs [Thyroid Receptor Associated Proteins]- (Figure 3).

In the cytoplasm activated MEK also tyrosine phosphorylates STAT1α and STAT3, resulting in their activation and nuclear translocation, further serine phosphorylation of these STATs by the nuclear MAPK maximizes the STAT transcriptional activity [12].

Phospholamban and Cardiac Effects

Myocardial contraction and relaxation are mediated through the release and re-uptake of calcium, respectively. Some abnormalities of cardiac function in patients with thyroid dysfunction directly reflect the effects of TH on calcium activated ATPase and Phospholamban [PLB] which are involved primarily in the regulation of systodiastolic calcium concentrations in cardiomyocytes. Calcium re-uptake is dependent on the action of Sarcoplasmic Reticulum Ca^{2+}-ATPase [SERCA], which is normally inhibited by PLB; moreover, PLB is a major substrate for the cAMP-dependent protein kinase located in the cardiac muscles, but it is also expressed in slow twitch skeletal muscle and smooth muscle cells. In the cardiac muscle, PLB indirectly controls the activation of SERCA. In the unphosphorylated state, PLB is an inhibitor of cardiac muscle SERCA; however, when PLB is phosphorylated, there is no inhibition. This is lack of inhibition results in the activation of SERCA, which leads to enhanced muscle relaxation rates, and contributes to the inotropic response. In addition, PLB activity is regulated by two phosphoproteins, the inhibitor-1 of protein phosphatase 1 and the small heat shock protein 20, which affect the overall SERCA-mediated calcium-transport [13,14]. Finally, TH up-regulates expression of SERCA and down-regulates PLB expression, thereby enhancing myocardial relaxation. Moreover, the improved calcium reuptake during diastole may have a favorable effect on myocardial contractility. Actually, the greater end-diastolic reduction in cytoplasmic concentration of calcium increases the magnitude of the systolic transient of calcium that, in turn, augments its availability for activation of tropomyosin units [15,16].

Cardiovascular Involvement in Hyperthyroidism

Excess TH has pronounced cardiovascular manifestations (Table 1). Overall, hyperthyroidism is characterized by an increase in resting heart rate [at least half the patients with hyperthyroidism have sinus tachycardia exceeding 100 beats/min] blood volume, stroke volume, myocardial contractility and ejection fraction, and an improvement in diastolic relaxation. An increase in TH level induces resting tachycardia; palpitations are one of the most-common symptoms associated with overt hyperthyroidism, and about 20% of hyperthyroid patients overall have AF. The rapid and irregular heartbeat produced by AF increases the risk of blood clot formation inside the heart. These clots may eventually become dislodged, causing embolism, stroke and other disorders. Since symptoms of hyperthyroidism are often non-specific and develop slowly, the AF may be the first clinical manifestation of thyroid dysfunction [17]. The AF is usually persistent rather than paroxysmal, and is more probable in older patients - perhaps reflecting a reduction in the threshold for this arrhythmia with age- Pulse pressure is widened, cardiac output and sympathetic tone are increased, and a hyperkinetic apex beat and a loud first heart sound are described; in addition, an accentuated pulmonic component of the second sound can be noticed frequently. Second or third degree heart block complicating hyperthyroidism is rare, and has most commonly been reported in association with acute inflammatory disease, hypercalcemia, administration of drugs [for example digoxin], or co-existing heart disease. Actually, the evidence from the sporadic reported cases suggests that any part of the cardiac conduction system is vulnerable to the effects of the elevation of TH, such effects can manifest as sick sinus syndrome, sinoatrial block, or various degrees of AtrioVentricular [AV] block. The data in the literature that address the pathogenesis of high-grade AV block in the context of hyperthyroidism are primarily speculative [18,19].

The increase in chronotropism and batmotropism is probably caused by imbalanced sympathovagal tone due to a relative rather than an absolute adrenergic overdrive. The strong inotropic activity of

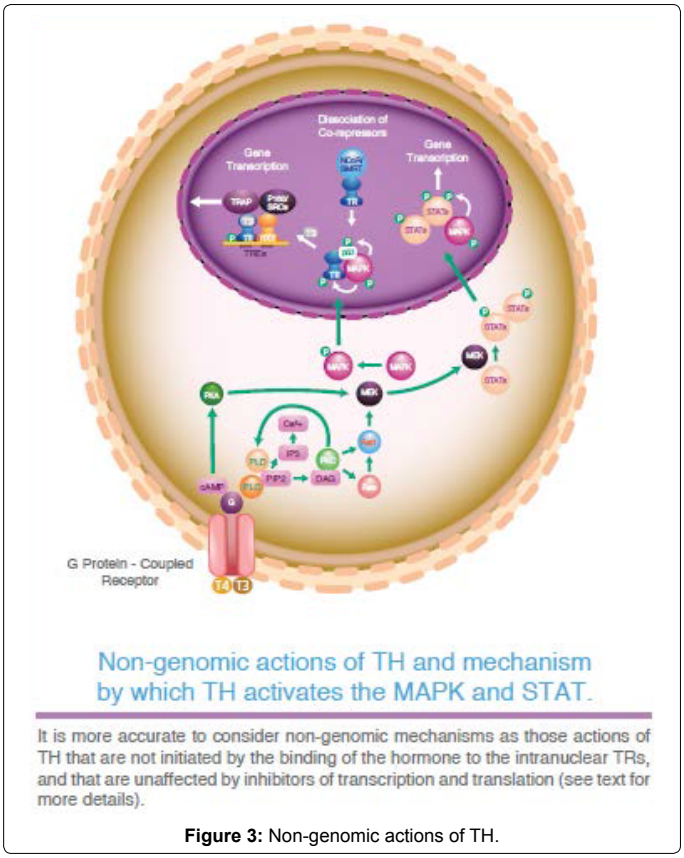


Figure 3: Non-genomic actions of TH.

Reduction of the systemic vascular resistance	Increase in cardiac output
Decrease in renal perfusion	Increase in heart rate
Decrease in diastolic arterial pressure	Increase in pulse amplitude
Decrease in afterload	Increase in stroke volume
Improvement in diastolic relaxation	Increase in ANP secretion
Peripheral vasodilation	Increase in blood volume
Tachyarrthymias	Increase in preload
Alteration of cardiac myofibril contractility	Increase in renal blood flow
Concentric cardiac hypertrophy	Increase in systolic arterial pressure
Pre mature trail heart beats	Increase in myocardial contractility
Low interatrial difference of action potential duration	Increase in LV systolic function
Reduced functional cardiac reserve and physical load tolerance	Increase of end-diastolic left ventricular volume
Pulmonary hypertension	Increase of number of β1-adrenoreceptors
Delay in intraventricular conduction	Increased risk of total mortality
Prolongation in intra-atrial conduction	Increased risk of Cardiovascular Disease
Increase in sympathetic tone	Increased risk for Heart Failure Events

Table 1: Cardiac and Hemodynamic consequences of hyperthyroidism.

TH is probably due to an increased number of β-adrenergic receptors. Circulating catecholamine levels are in fact the same, but G protein and β-receptors increase; the sensitivity of the cardiovascular system to adrenergic stimulation is not changed by TH, and the changes in the heart rate result from both an increase in sympathetic tone and decrease in parasympathetic tone. Alterations in the pulse and heart sounds are common, as is also the case with the Means-Lerman "scratch" [mid-systolic and end-tidal murmur heard at the left upper sternal border thought to occur from rubbing of the pericardium against the pleura, which may sound like a pericardial friction rub as seen in pericarditis]. Left Ventricular [LV] systolic function is consistently increased at rest and the rate of LV chamber relaxation and LV filling is increased. Cardiac remodeling includes alterations in molecular, cellular, and interstitial systems contributing to changes in size, shape, and function of the heart. TH serve as regulators for diverse remodeling processes of the cardiovascular system, promote a beneficial cardiomyocyte shape and improve contractility, relaxation, and survival via reversal of molecular remodeling. T3 and T4 reduce fibrosis by decreasing interstitial collagen and reduce the incidence and duration of arrhythmias via remodeling ion channel expression and function. TH restores metabolic function and also improves blood flow both by direct effects on the vessel architecture and decreasing atherosclerosis [20]. Finally, TH directly affects cardiac myocytes by regulating genes important for myocardial contraction and electrochemical signaling, including positively regulating of SERCA, α-myosin heavy chain, β1-adrenergic receptors, guanine nucleotide regulatory proteins, Na^{+}-K^{+}-ATPase, and voltage-gated potassium channels and negatively regulating β-myosin heavy chain, PLB, Na^{+}-Ca^{2+} exchanger, and adenylyl cyclase types V and VI. Additionally, systolic arterial pressure is increased and diastolic arterial pressures is decreased, so that pulse pressure is particularly wider and mean arterial pressure is usually decreased, with a remarkable increase in cardiac output and a notable reduction in peripheral vascular resistance. However, hyperthyroidism has only minor effects on mean arterial blood pressure, because of increases in systolic pressure - caused by increased stroke volume- and decreases in diastolic pressure due to peripheral vasodilatation. The peripheral vascular effects result from a TH-mediated decrease in systemic peripheral resistance, induced by dilating arterioles and by increased metabolic rate in peripheral tissues. As a rule, the total peripheral vascular resistance decreases in thyrotoxicosis, and these alterations may be mediated by changes in non-thyroid hormones which affect the vasculature [21,22]. Even though in thyrotoxicosis plasma catecholamines are unchanged or low, the β-adrenergic receptor density is altered in a time and tissue-dependent manner, raising tissue sensitivity to catecholamines. The rapid use of oxygen, increased production of metabolic end-products, and relaxation of arterial smooth muscle fibers by TH cause peripheral vasodilatation, leading to a reduction in peripheral vascular resistance, and contributing to a further increase in heart rate; concomitantly there is a selective blood flow increase in some sites such as the skin, skeletal muscles and heart, and a fall in diastolic pressure with a simultaneous widening of pulse pressure. The vasodilatation present and the lack of an increase in renal blood flow generate a reduction in renal perfusion pressure, with activation of the RAAS, which increases sodium retention and blood volume (Figure 4). These changes result in preload increase and afterload reduction, leading to a significant increase in stroke volume [23,24]. Human cardiomyocytes produce and secrete a family of related peptide hormones such as Atrial Natriuretic Peptide -ANP- and Brain Natriuretic Peptide -BNP- which have potent diuretic, natriuretic and vascular relaxing effects. They also have other effects, the most important being: decrease blood pressure, increase natriuresis and diuresis and inhibit the release or action of several hormones including those of RAAS, endothelin and vasopressin. ANP is released into circulation in response to increased atrial distension or stretching. Furthermore, it has been shown that the production of ANP is increased by hormonal factors including TH. In addition, TH stimulates both the synthesis and release of BNP; thus, serum BNP levels are also affects in thyrotoxicosis.

A higher cardiac preload may trigger secretion of ANP; however, it is suggested that TH-induced myocardial ANP secretion in healthy subjects is not the result of a direct action on the myocardium, but rather the result of an indirect modification in cardiovascular hemodynamic leading to increased atrial stretch. Therefore, hyperthyroidism is characterized by a high cardiac output state with a remarkable increase in heart rate and cardiac preload and a reduction in peripheral vascular resistance, resulting in hyperdynamic circulation (Figure 5). Moreover, increased pressure in the left atrium increases pressure in

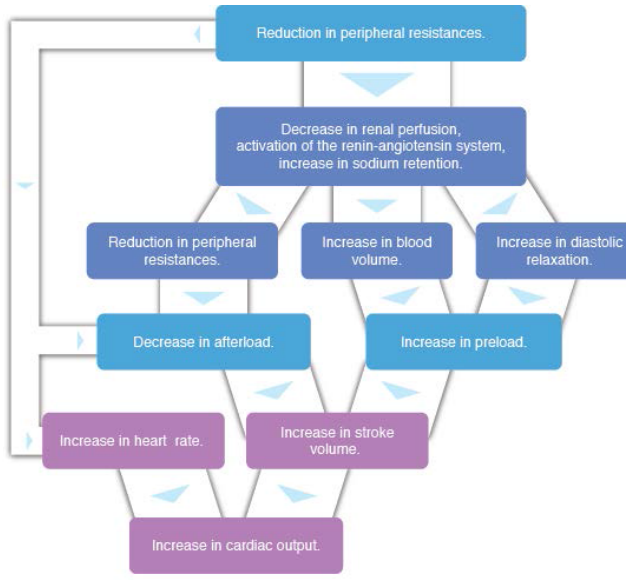


Figure 4: Changes leading to hyperdynamic circulation in hyperthyroidism.

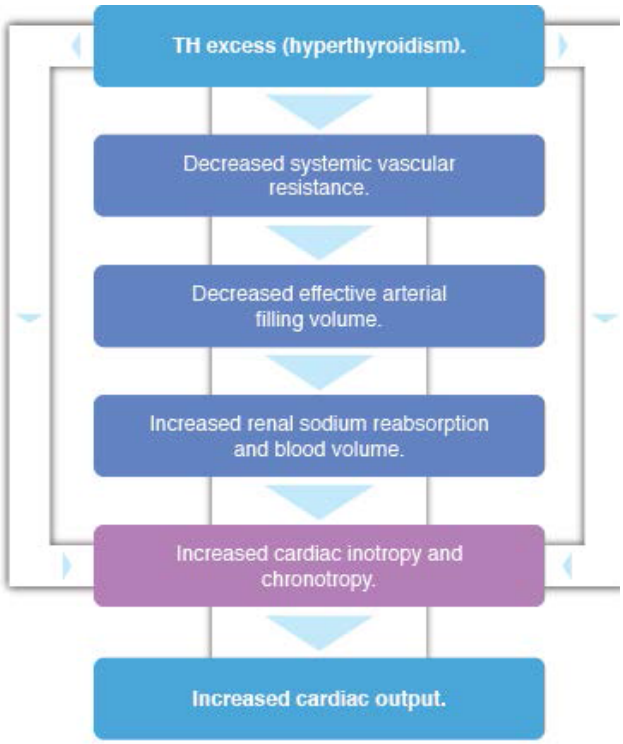


Figure 5: Increase in cardiac output mediated by TH excess (hyperthyroidism).

the pulmonary veins, and this in turn causes reflex contraction of the arterioles in the lesser circulation [Kitaev's reflex] due to stimulation of baroreceptors. Spasm in the arterioles produces a significant increase in pulmonary artery pressure to intensify the load on the right ventricle, which needs contact with a greater force in order to eject blood into the pulmonary trunk, leading to the increase of pulmonary resistance and pulmonary hypertension. Several mechanisms have been suggested in the pathogenesis of pulmonary artery hypertension in patients with hyperthyroidism, including an autoimmune process associated with endothelial damage or dysfunction; other possible mechanisms include: increased cardiac output; enhanced catecholamine sensitivity, reduction in pulmonary vascular compliance, increase in vascular resistance; increased metabolism of intrinsic pulmonary vasodilating substances, and decreased or impaired metabolism of vasoconstrictors [all this with normal pulmonary artery resistance]. Although the mechanism is uncertain, the reversal of pulmonary artery hypertension following restoration to a euthyroidism state supports a causal relationship. A possible explanation includes an influence of TH, which affects growth and maturation of vascular cells, and enhanced catecholamine sensitivity, causing pulmonary vasoconstriction. Therefore, pulmonary artery hypertension should be considered in hyperthyroid patients with dyspnea.

Cardiovascular Involvement in Hypothyroidism

A deficiency in TH compromises the function of the cardiac muscle by decreasing the activity of enzymes involved in the regulation of calcium uptake and the expression of several contractile proteins in cardiomyocytes, resulting in lower heart rate and weakening of myocardial contraction and relaxation. The most obvious effect of TH deficiency on the heart is a prolongation of both systolic and early diastolic time characteristics [25,26]. In the hypothyroid heart, in contrast to congestive heart failure, pulmonary pressure is not increased; hypothyroid patients have reduced cardiac output, stroke volume and plasma volume. Even though hypothyroidism causes fewer cardiovascular symptoms and signs, it is associated with bradycardia, increased vascular resistance, narrow pulse pressure and mild hypertension. Circulation time is prolonged, but right and left heart filling pressures are usually within normal limits, unless they are elevated by Pericardial Effusion [PE]. Venous pressure is normal, but peripheral resistance is increased; there is a redistribution of blood flow with marked reduction in cerebral, renal and cutaneous flow. Cardiac oxygen consumption is reduced even further than what is anticipated from the decreased work load, making for an energy-efficient state of cardiac contraction. However, congestive heart failure has been described in severely hypothyroid patients without underlying heart disease. Measurements of isovolumetric relaxation time reveal a prolongation of this interval [27,28]. In addition, there is prolongation of the pre-ejection period and an increased pre-ejection period to LV ejection time ratio (Table 2). Myocardial work efficiency is lower than in normal subjects. Angina pectoris, diastolic hypertension, AV blocks, and pericarditis are major cardiovascular complications in a hypothyroid state. Diastolic dysfunction both at rest and on exertion is the most uniformly found cardiac abnormality in patients with hypothyroidism; LV diastolic function is altered, with a slowed myocardial relaxation and impaired early ventricular filling. This is frequently associated with a fluctuating impairment in LV systolic function even at a very early stage. LV asynchrony is defined as deterioration of the simultaneous contraction of corresponding cardiac segments; as a result, delayed activation of some ventricular segments leads to uncoordinated contraction. LV asynchrony may affect diastolic and systolic function, exercise capacity, prognosis, quality of life, and symptoms of heart failure, worsening the heart failure. LV systolic function is marginally subnormal, with slightly lower ejection fraction and stroke volume values [29,30]. Preload is reduced, with a subnormal cardiac output. High cholesterol levels are an additional risk for the development of atherosclerosis. Alterations in the pulse and peripheral vasoconstriction may be observed, such as prolongation of the QRS complex and the QT interval [the QT interval reflects traditional electrocardiographic parameter of the duration of ventricular repolarization] with an increased risk of developing ventricular tachyarrhythmias. QT dispersion is the inter-lead variability of the QT interval on surface electrocardiogram, reflecting

Narrow pulse pressure	Decrease in stroke volume
Increase in diastolic arterial pressure	Dcrease in preload
Atrioventricular blocks	Decrease in blood volume
Peripheral vasoconstriction	Decrease in cardiac output
Ventricular tachyarrthymias, because of bradycardia and hypothermia	Reduction in exersize tolarence
Pericarditis	Reduction in myocardial contractilty
Pericardial tamponade	Bradycardia
Negative chronotropic and inotropic state	Increased risk of all-cause moratility and cardiovascular disease death
Prolongation of QT interval	Increased risk of heart failure events
Impaired left ventricular systolic synchronization	Increase in peripheral vascular resistance
Prolongation of the isovolumetric relaxation time	Decrease in LV systolic function
Flattened to inverted T waves	Right bundle branch block
Increase in the QT dispersion	Increase in the arterial stiffness
Decreased amplitude of p wave	Left ventricular Posterior wall thickness

Table 2: Cardiovascular and Hemodynamic changes in hypothyroid stage.

regional variations in myocardial repolarization. Increased QT dispersion has been linked to the occurrence of malignant ventricular arrhythmias and sudden cardiac death; clinical observations show that ventricular arrhythmias and sudden death are uncommon in hypothyroidism, despite the marked prolongation of the QT interval. However, increased QT dispersion in hypothyroidism may facilitate ventricular arrhythmias with hypokalemia, hypomagnesemia, long QT syndrome, and sudden cardiac death. Other findings are: incomplete or complete right bundle branch block, decreased p wave amplitude, diffuse flattening or inversion of T waves together with a generalized low voltage of all the complexes. The T wave is dome-shaped and partially obliterates the ST segment ["the mosque sign"]. Isolated myxedema may cause heart failure, PE and Pericardial Tamponade [PT], especially in subjects with profound T4 deprivation; PE in hypothyroidism is common and the mechanisms of myxedematous PE are increased permeability of capillaries with subsequent leakage of protein rich fluid into the interstitial space, impaired lymphatic drainage, and salt and water retention; nevertheless, an effusion which causes cardiac tamponade is rarely seen. PT in hypothyroid patients with PE is attributed to the slow accumulation of fluid and the remarkable compliance of the pericardium. The incidence of PE in patients with severe hypothyroidism ranges from 30% to 80%, and the incidence in mild hypothyroidism ranges from 3% to 6%.

Electrocardiogram [ECG] characteristics of PE in hypothyroidism include low QRS voltage, PR-segment depression, ST-segment deviation, T-wave changes and electrical alternans. Moreover, the heart in overt myxedema is often flabby, and grossly dilated. Classic findings of overt myxedema are: cardiac enlargement, dilatation, significant bradycardia, weak arterial pulses, hypotension, distant heart sounds, low *ECG* voltage, non-pitting edema and evidence of congestive heart failure.

There is a relationship between hypothyroidism and coronary artery disease, either because of the presence of a negative chronotropic and inotropic state or the presence of hypercholesterolemia and hypertension, with an increased risk of atherogenesis; but otherwise, TH are powerful regulators of vasculature in the adult myocardium; therefore, a low free T3 [fT3] state would inhibit neovascularization in cardiac tissue after acute myocardial infarction, which would accelerate cardiac pathologic remodeling and heart failure, leading to short-term and long-term adverse cardiac events [31,32].

Heart Failure in Hyperthyroidism

Besides its metabolic and thermoregulatory tissue effects, TH regulates cardiac performance by acting on the heart and vascular system. Hyperthyroid patients can manifest findings of congestive heart failure in the absence of prior cardiac injury. Diastolic and systolic functions are clearly modified by TH; ventricular contractile function is also altered by changes in the hemodynamic pattern, secondary to TH effects on peripheral vascular tone. TH equilibrium preserves positive ventricular-arterial coupling, leading to an adequate balance for cardiac work. Hemodynamic alterations due to hyperthyroidism decrease myocardial contractile reserve and do not allow further increases in ejection fraction and cardiac output on exertion, probably because of the inability to reduce the already low peripheral vascular resistance, while constriction of venous vessels increases. The resulting decrease in peripheral vascular resistance activates the RAAS, leading to retention of sodium and fluid [33,34]. The forced increase in preload and total blood volume increases cardiac work and stimulates the development of myocardial hypertrophy. However, the increase in preload and blood volume leads to a rise in ventricular filling pressure, and to a moderate degree of pulmonary and peripheral congestion. Cardiac output is augmented by a higher heart rate and increased stroke volume, facilitating the return of blood to the heart; these changes result in increased mean circulatory filling pressure, which promotes retrograde blood flow to the right atrium; TH also increases erythropoiesis, and the net effect is an increase in total blood volume and stroke volume. The transcriptional effects lead to increased contractility through effects on the release and uptake of sarcoplasmic reticular calcium and phosphorylation of phospholamban. The non-transcriptional effects are induced by the effect of TH on various ion channels [35,36]. All these cardiac effects, along with low peripheral vascular resistance and increase in total blood volume, lead to a high cardiac output state [often called "high-output heart failure"]. However, "heart failure" is not really the appropriate term because cardiac output is increased, although congestive circulation is present (Table 3). The tachycardia observed in hyperthyroidism appears to be due to a combination of increased rate of diastolic depolarization and decreased duration of the action potential in the sinoatrial nodal cells. On the other hand, the development of "high-output heart failure" in hyperthyroidism may be due to "Tachycardia-Mediated Cardiomyopathy" [TMC]. A high cardiac output has been described as being >8 L/min or a cardiac index >3.9 L/min/m^2. TMC is defined as secondary ventricular dysfunction due to chronic tachycardia, which is fully or partially recoverable after heart rate normalization; the diagnosis should be suspected in patients with compromised ventricular function in the course of a ventricular or supraventricular tachycardia. The diagnosis can only be established with the recovery of ventricular function once the tachycardia and the thyrotoxic state are under control [37,38]. While TMC usually presents with significant cardiac enlargement, reduced ventricular wall thickness, and impaired ventricular contraction similar to dilated cardiomyopathy, the cardiac abnormalities normalize with control of the tachyarrhythmia and heart failure. Actually, It has been proposed that cardiovascular effects of hyperthyroidism, i.e., tachycardia, increased cardiac output, systolic hypertension, and myocardial contractility are the result, not only of increased activity of the sympatho-adrenal system, but also of increased cardiac tissue responsiveness to catecholamines, with up-regulation of beta adrenergic receptors (Figure 6).

The term "Thyrotoxic cardiomyopathy" defines myocardial damage caused by the toxic effects of abundant TH, resulting in altered energy production by myocytes [oxidative phosphorylation, glycolysis], intracellular metabolism [protein synthesis] and myofibril contractile function. The main manifestations are left ventricular hypertrophy, heart rhythm disturbances -usually, AF- dilation of the heart chambers and heart failure, pulmonary hypertension, and diastolic dysfunction. It is not known whether cardiomyopathy in hyperthyroidism is secondary to direct toxic effects of excess TH, whether it results from the hyperdynamic or high-output stress caused by the TH, or whether it is caused by a combination of both. However, cardiomyopathy caused by hyperthyroidism has been shown to be reversible in adults with anti-thyroid therapy. Factors which may play a role in recovery

Persistent Tachycardia	Decrease in peripheral vascular resistance
Increase in cardiac preload	Increase in ventricular filling pressure
Increase in pulmonary arterial pressure	Increase in total blood volume
Absence of Underlying heart disease	Increase in activity of the sympatho-adrenal system and increase in cardiac tissue responsiveness to catecholamines

Table 3: Characteristics that define "high-output heart failure" in hyperthyroidism.

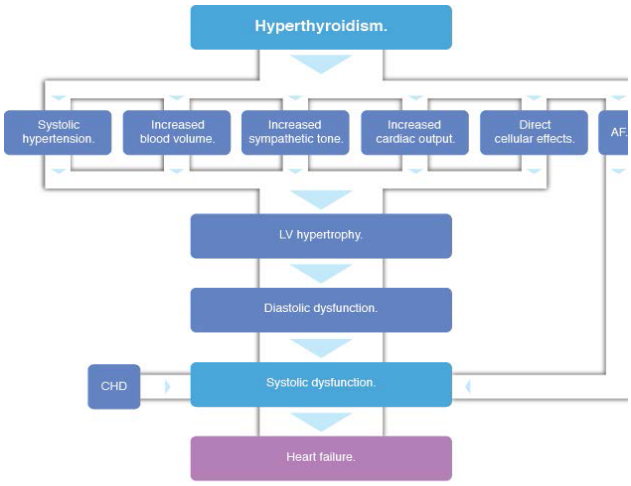


Figure 6: Components leading to heart failure in hyperthyroidism.

are β-blocker administration and high T3 serum levels. Three stages of thyrotoxic cardiomyopathy are defined:

1. *Hyperkinetic*: In which left ventricular function is preserved, but left ventricular ejection fraction does not increase with exertion.

2. *Normokinetic:* It is a compensatory stage, where there is a reversible myocardial hypertrophy with preserved cardiac output.

3. *Hypokinetic:* It is a decompensation stage, where there is low cardiac output and stroke volume, reversible or irreversible heart chamber hypertrophy and dilation.

Moreover, "right ventricular heart failure" may result from right ventricular volume overload, due to the increased blood volume and venous return. It is characterized by right ventricular dilation, enlargement of the tricuspid valve annulus and tricuspid insufficiency, and is frequently associated with pulmonary hypertension.

Proposed mechanisms include high cardiac output-induced endothelial injury, increased metabolism of intrinsic pulmonary vasodilating substances resulting in elevated pulmonary vascular resistance; therefore, hyperthyroidism should be included in the causes of unexplained right heart failure [39,40].

Heart Failure in Hypothyroidism

Cardiac changes in hypothyroidism are the complete opposite of those occurring in thyrotoxicosis. The most prominent findings are the decrease in cardiac output and cardiac contractility, diastolic hypertension, increased systemic vascular resistance, and rhythm disturbances; systolic and diastolic functions are reduced at rest and during exercise. TH deficit decreases tissue thermogenesis and increases resistance in peripheral arterioles through the direct effect of T3 on vascular smooth muscle cells. Cardiac preload is decreased due to the impaired diastolic function and to the decreased blood volume (Table 4). Cardiac afterload is increased and chronotropic and inotropic functions are reduced, resulting in a decrease in cardiac output [41,42]. The physiological chronotropic response and normal tension of the heart muscle in diastolic phase depend on the proper expression of T3 in the heart cells and its stimulating influence on Na^+-K^+-ATPase and Ca^{2+}ATPase in the endoplasmic reticulum. The isovolumetric relaxation phase of diastolic function slows down, just like the contraction velocity during systole, and there is chamber dilatation and impaired myocardial blood flow.

Dilated Cardiomyopathy [DCM] is a heart muscle disorder defined by the presence of a dilated and poorly functioning left ventricle in the absence of abnormal loading conditions [hypertension, valve disease] or ischemic heart disease sufficient to cause global systolic impairment; in hypothyroidism, although cardiac output is reduced, heart failure is relatively rare because there is a lower oxygen demand in the periphery. The improvement of the cardiac function after hormonal treatment is an important argument in favor of the implication of hypothyroidism in the genesis of DCM [43,44]. "Low T3 Syndrome" [LTS] is characterized by an isolated reduction of T3, with normal serum levels of TSH and T4, the principal pathophysiological mechanism underlying low circulating T3 is the reduced enzyme activity of 5'monodeiodinase, responsible for converting T4 into T3 in peripheral tissues. Although LTS was once considered a beneficial adaptive mechanism under conditions of stress, in patients with heart failure LTS alters cardiac function by several mechanisms [from abnormal expression of genes encoding myocardial contractile proteins and cardiac ion channels to QT interval prolongation]. A typical pattern of altered TH metabolism characterized by low T3 circulating levels has been described in patients with acute myocardial infarction and heart failure and in adults after cardiopulmonary bypass. LTS is a strong predictor of death in cardiac patients and might be directly implicated in the poor prognosis of cardiac patients (Figure 7).

Atrial Fibrillation and Thyroid Dysfunction

AF is the most common cardiac complication of hyperthyroidism, occurring in an estimated 10% to 25% of overtly hyperthyroid patients; in comparison, 0.4% of the general population has AF, representing an independent risk factor for cardiovascular events. Prevalence increases with age, so much so that 25% of hyperthyroid patients older than 60 years had AF compared to 5% in patients less than 60 years of age, indicating that age is a major factor in the onset of AF. The propensity to develop AF may be due to the shortened refractory period of atrial cells and a greater delay in the rectifier potassium current increases between the right atrium and the left atrium, creating a substrate for AF [45,46].

Furthermore, TH potentiates the effect of the adrenergic system on the heart, and while catecholamine levels are either normal or decreased in hyperthyroidism, catecholamine action occurs through increased tissue sensitivity due to up-regulated transcription of beta-adrenergic receptors and differences in autonomic innervations between atria and ventricles. It is also possible that the sensitivity of atrial or ventricular myocardial cells to TH is different. Reentry has been postulated as one of the main mechanisms leading to AF. Multicircuit wave fronts that are generated in the atrium could disturb normal sinus rhythm and set up a fibrillatory rhythm. According to wavelength concepts, AF is more likely if effective refractory periods are short and conduction is slow. Hyperthyroidism is associated with shortening of action potential duration. Action potential duration determines the refractory period and is therefore a key determinant of the likelihood of reentry.

Generally, the onset of AF occurs with premature complexes originating from the pulmonary veins, and the persistence of AF requires re-entry; premature complexes occurs secondary to automaticity or triggered activity. Hyperthyroidism is associated with reduced vagal

Bradycardia	Impaired systolic function
Decreased Cardiac preload	Impaired diastolic function
Increased systemic vascular resistance	Impaired left ventricular diastolic filling
Increase in left ventricular mass	Pericardial effusion

Table 4: Components leading to heart failure in hypothyroidism.

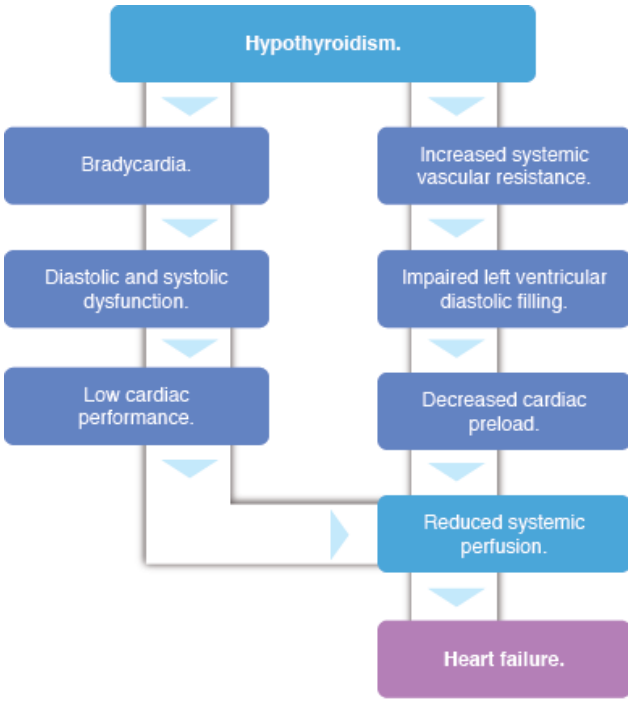


Figure 7: Components leading to heart failure in hypothyroidism.

activity and reduced heart rate variability; the rapid and irregular heartbeat produced by AF increases the risk of blood clot formation inside the heart. These clots may eventually become dislodged, causing embolism. Moreover, TH has various effects on coagulation. TH excess is associated with coagulation abnormalities, such as shortened activated partial thromboplastin time, increased fibrinogen levels, and increased factor VIII and factor X activity in patients in sinus rhythm with thyrotoxicosis. Recently, was determined whether history of thyroid dysfunction is a thromboembolic risk factor in patients with AF. Patients with AF in an academic institution between 2000 and 2010 were identified and followed-up. Clinical events [stroke/systemic embolism, bleeding, all-cause death] were recorded and related to thyroid status and disorders. Among 8962 patients, 141 patients had a history of hyperthyroidism, 540 had a history of hypothyroidism, and 8271 had no thyroid dysfunction. A total of 715 strokes/systemic embolism were recorded, with no significant difference in the rates of these events in patients with a history of thyroid dysfunction versus those without thyroid problems. There were 791 bleeding events; history of hypothyroidism was independently related to a higher rate of bleeding events. No significant difference among the 3 groups was observed for the incidence of death. History of hyperthyroidism was not an independent risk factor for stroke/systemic embolism in AF, whereas hypothyroidism was associated with a higher risk of bleeding events. These data suggest no additional benefit from the inclusion of thyroid dysfunction in thromboembolic prediction models in AF [47,48].

AF alters atrial electrical and structural properties in a way that promotes its own maintenance; this increases the risk of recurrence and may alter the response to antiarrhythmic drugs. The risk factors for AF in patients with hyperthyroidism are similar to those in the general population [age, ischemic heart disease, congestive heart failure, male sex and valvular heart disease]. However, other factors have been associated with the presence of AF in hyperthyroidism (Table 5) including obesity, chronic kidney disease [which is a powerful predictor of new-onset AF in hypertensive patients, independently of LV hypertrophy and left atrial dilatation], proteinuria, female sex, serum free T4 concentration, elevated transaminase concentrations and high sensitive C reactive [49,50].

Meantime, hypothyroidism is associated with bradycardia, decreased variability in heart rate, and has been associated with a lower risk of AF compared with euthyroid patients. Recently, associations between hypothyroidism and 10-year risk of incident AF was evaluated among 5069 Framingham heart Study participants; after excluding those with missing TSH, TSH <0.45 μIU/mL [hyperthyroid], TSH >19.9 μIU/mL, or prevalent AF. TSH was categorized by range [≥0.45 to <4.5; 4.5 to <10; 10 to ≤19.9 μIU/mL] and by quartiles. In categorical analysis, using TSH ≥0.45 to <4.5 μIU/mL as the referent, there was no association between hypothyroidism and 10-year AF risk. Comparing the highest [2.6 < TSH < 19.9 μIU/mL] to lowest [0.45 < TSH < 1.3 μIU/mL] quartiles of TSH further did not identify a significant association between TSH levels and 10-year risk of AF [51,52].

Subclinical Thyroid Dysfunction [SCTD] and cardiovascular disease and mortality

Although it is recognized that patients with SCTD may have subtle symptoms of thyroid dysfunction, the definition is purely a biochemical one: SCTD is defined as serum free T4 and total or free T3 levels within their respective reference ranges in the presence of abnormal serum TSH levels. Serum TSH is undetectable or low in Subclinical Hyperthyroidism [SHyper], and it is increased in Subclinical Hypothyroidism [SHypo]. It is a common finding in the growing population of elderly patients, occurring in 10-15% among those aged 65 and older [53,54].

Controversy persists about whether screening and treating subclinical thyroid dysfunction is warranted. SHypo has been associated with elevated cholesterol levels and increased risk for atherosclerosis, endothelial dysfunction, higher insulin levels and insulin resistance, which correlates positively with TSH levels and negatively with T3 and T4. Other factors contributing to endothelial damage are: low grade chronic inflammation and oxidative stress -through specific molecular pathways in endothelial cells, causing elevated levels of Nitric Oxide [NO]-. NO is synthetized enzymatically from l-arginine [l-Arg] by three NO synthase isoforms, iNOS, eNOS and nNOS. The synthesis of NO is selectively inhibited by guanidino-substituted analogs of l-Arg or methylarginines such as Asymmetric DimethylArginine [ADMA], which results from protein degradation in cells. In endothelial cells, hyperlipidemia can disturb the NO synthesis pathway by increasing levels of ADMA, possibly by reducing enzyme Dimethylarginine Dimethylaminohydrolase [DDAH] activity; increased plasma ADMA concentrations cause impaired NO synthesis leading to endothelial dysfunction and atherosclerotic vascular disease. Oxidant stress indicates an imbalance between the oxidant and antioxidant substance, during which Reactive Oxygen Species [ROS], and their

Classic Factors	Novel Factors
Age>60 years	Obesity
Ischemic heart disease	Chronic kidney disease
Congestive heart failure	Proteinuria
Male sex	Elevated transaminase concentrations
Cardiac valve disease	Elevated sensitive c reactive protein
TSH levels <0.1 μIU/ml	Serum free T4 concentration
	Female sex
	Cardiac frequency >80 beats/min

Table 5: Risk factors for AF in patients with hyperthyroidism.

derivatives, exceeds endogenous antioxidant defense mechanisms. Inflammation is an important cause of oxidative stress as enzymatic systems producing a large amount of ROS; including xanthine oxidase, Nicotinamide Adenine Dinucleotide [NADH] and NADH Phosphate Oxidase [NOX], which are induced by inflammatory stimuli. Since ROS reacts with NO extremely readily, producing even more harmful reactive nitric intermediates, minimum oxidative stress in endothelial cells can uncouple NO synthesis and will be devastating to endothelial function (Figure 8). These aspects affect specific molecular pathways in endothelial cells and cause elevated levels of NO and other molecular changes, characteristic of endothelial dysfunction, resulting in atherosclerosis and CHD.

For SHypo, combined available data from large prospective cohorts suggest that SHypo is associated with an increased risk of CHD in those with higher TSH levels. The risk of both CHD mortality and CHD events, but not of total mortality, increases with higher concentrations of TSH, and is significantly elevated in adults with TSH levels of 10 μIU/mL or greater [55,56].

Moreover, SHyper in age and sex-adjusted analyses was associated with increased total mortality, CHD mortality, CHD events and AF. Risks did not differ significantly by age, sex, or preexisting cardiovascular disease, and were similar after further adjustment for cardiovascular risk factors, with an attributable risk of 14.5% for total mortality and 41.5% for AF. However, heart failure is the leading cause of an increased cardiovascular mortality in both overt and SHyper.

Risks for CHD mortality and AF [but not other outcomes] were higher for thyrotropin levels under 0.10 μIU/mL compared with thyrotropin levels between 0.10 and 0.44 μIU/mL.

In summary, in original cohort studies with a systematic review and pooled individual data from over 70.000 individuals with SCTD was found that SHypo and SHyper are associated with increased risk of cardiovascular outcomes compared to euthyroid state, particularly in those with a more pronounced thyroid dysfunction. Specifically, SHypo is associated with an increased risk of CHD events, CHD mortality and heart failure events in individuals with higher TSH levels, particularly in those with TSH levels ≥10 μIU/mL. Conversely, SHyper is associated with an increased risk of total mortality, CHD mortality, heart failure and AF, particularly in those with suppressed TSH levels <0.10 μIU/mL [57,58].

Recently, in a large-scale, population-based cohort with long-term follow-up [median 7.4 years], a single abnormal serum TSH measurement and an increasing duration of decreased or elevated serum TSH were strong risk factors for mortality. When combining the TSH measurement with T3 and T4 measurements, overt and subclinical hyperthyroidism and overt but not subclinical hypothyroidism were associated with increased mortality [59].

In another study was evaluated the risk of all-cause mortality, Major Adverse Cardiovascular Events [MACEs], and cause-specific events in subjects with overt and subclinical thyroid dysfunction. All-cause mortality, MACEs, and cause-specific events identified in nationwide registries were measured. All-cause mortality, MACEs, and cause-specific events identified in nationwide registries were measured. A total of 47.327 deaths occurred among 563.700 included subjects [mean age 48.6 [SD ± 18.2] y; 39% males]. All-cause mortality was increased in overt and subclinical hyperthyroidism compared with euthyroid people. Risk of MACEs was elevated in overt and subclinical hyperthyroidism. A reduction of all-cause mortality was observed in subclinical hypothyroidism with TSH of 5-10 μIU/mL; moreover, it was also shown that the heart failure is the leading cause of an increased cardiovascular mortality in both overt and subclinical hyperthyroidism (Figure 9) [60].

Amiodarone and Thyroid

Amiodarone is a potent class III anti-arrhythmic drug used in clinical practice for the prophylaxis and treatment of many cardiac rhythm disturbances, ranging from paroxysmal AF to life-threatening ventricular tachyarrhythmias. Amiodarone often causes changes in thyroid function tests mainly related to the inhibition of 5'-deiodinase activity resulting in a decrease in the generation of T3 from T4, with a resulting increase in rT3 production and a decrease in its clearance. However, the use of amiodarone is associated with several side-effects owing to its marked lipid affinity. It is highly concentrated in tissues and is linked to a number of adverse effects including photosensitivity, corneal microdeposits, pulmonary toxicity, hepatotoxicity, peripheral neuropathy, lung dysfunction, gynecomastia, ataxia, tremors, peripheral neuropathy, hyperthyroidism and hypothyroidism [61].

Amiodarone is a benzofuran derivative containing two atoms of iodine per molecule. This amount to 37.5% of organic iodine by molecular weight, and 10% of the drug's iodine content is released daily as free iodide. Drug doses range from 200 to 600 mg daily and treatment releases about 7-20 mg of iodide daily, which is about 50-100 fold the optimal daily iodine intake.

Although the majority of the adverse effects of amiodarone on several organs are due to deposition of the drug in the parenchyma, its effects on the thyroid gland can be divided into two groups: intrinsic effects resulting from the inherent properties of the compound, and iodine-induced effects due solely to the pharmacologic effects of a large iodine load - it has the potential to cause thyroid dysfunction because of its iodine-rich chemical structure (Table 6).

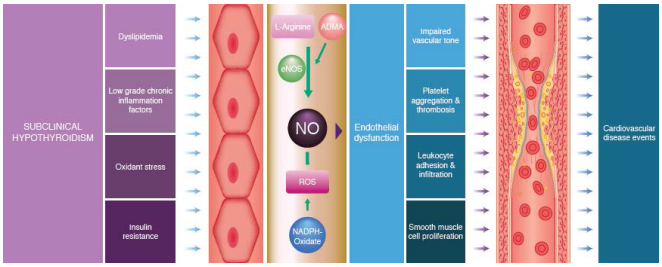


Figure 8: SHypo induces endothelial dysfunction and causes elevated levels of NO and other molecular alterations, resulting in atherosclerosis and cardiovascular events.

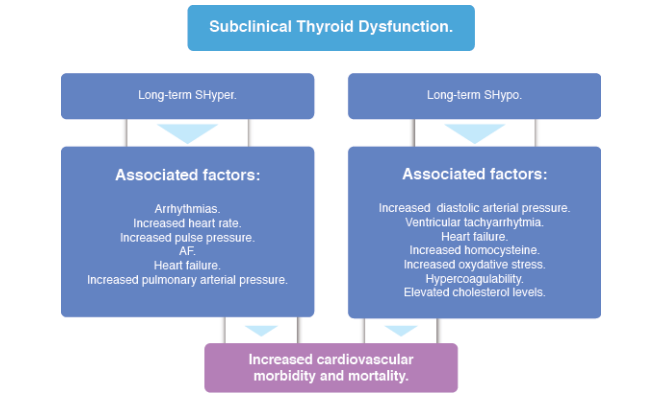


Figure 9: Sibclinical Thyroid Dysfunction and increased cardiovascular morbidity and mortality.

Amiodarone can lead to both hypothyroidism [Amiodarone-Induced Hypothyroidism -AIH- with a prevalence ranging from 10-20%] and, less commonly to hyperthyroidism [Amiodarone-Induced Thyrotoxicosis -AIT- with a prevalence ranging from 2-9.6%]. Most patients treated with amiodarone will remain euthyroid throughout the treatment course. The AIH is slightly more frequent in females, with a female to male ratio of 5:1. This occurs more frequently in iodine-sufficient areas, where AIH usually develops in patients with underlying Hashimoto thyroiditis; AIT appears to occur more frequently in geographical areas with low iodine intake, whereas AIH is more frequent in iodine-sufficient areas. The most likely pathogenic mechanism is that the thyroid gland is unable to escape from the acute Wolff-Chaikoff effect after an iodine load and to resume normal thyroid hormone synthesis [62]. The large amount of iodide released during the metabolism of amiodarone leads to an adaptive blockage of further thyroidal iodide uptake and TH biosynthesis [Wolff-Chaikoff effect]. Although it can be apparent within the first two weeks of treatment, further exposure to iodine leads to normal resumption of TH synthesis. This escape phenomenon from the Wolff-Chaikoff effect helps protect the individual from developing hypothyroidism. Alternatively, amiodarone may accelerate the natural course of Hashimoto thyroiditis via iodine-induced damage to the thyroid follicles [63]. The pharmacological concentrations of iodide associated with amiodarone treatment lead to a protective inhibition of thyroidal T4 and T3 synthesis and release by thyroid within the first two weeks of treatment. After 3 months of amiodarone administration, a steady state is reached, with some hormonal changes persisting indefinitely. Total and free T4 and rT3 remain at the upper end of normal or slightly elevated, and serum T3 levels remain in the low normal range. In contrast, serum TSH levels return to normal after 12 weeks of therapy. The cause for TSH normalization is presumed to be an increase in the T4 production rate, possibly as a result of increased intrathyroidal iodine stores and escape from the Wolff-Chaikoff effect [64].

The incidence of AIT is reported as 2-9.6% in most studies. It is relatively more frequent in iodine-deficient areas and particularly in men [male to female incidence ratio is 3:1]. AIT may develop early during amiodarone treatment or even several months after drug withdrawal due to its long half-life; two main mechanisms can lead to AIT: iodine-induced hyperthyroidism [type 1 AIT, a form of Jod-Basedow effect, which is identical to that seen in patients with endemic iodine deficient goiter who are given iodide replacement]; or destructive thyroiditis with destruction of thyroid follicles resulting in a thyroiditis with excess release of T3 and T4 [type 2 AIT], caused by amiodarone itself and its high iodine content. Type 1 AIT occurs in subjects with an abnormal thyroid [goiter or latent autoimmune disease], with the iodine load triggering autonomous TH production. Type 2 develops in subjects who have an apparently normal gland and may reflect TH release due to direct cytotoxic effects of the drug on thyrocytes. The nature of destructive thyroiditis is that of a self-limiting disease. AIT may develop early during amiodarone treatment or even several months after drug withdrawal. This is because of amiodarone and its metabolites -mainly desethylamiodarone- Recent data show that type 2 AIT is by far the most frequent form. However, the two mechanisms may coexist in the same patient -indefinite or mixed AIT- [65,66].

Dronedarone is a derivative of amiodarone that has had the iodine groups were removed and a methane sulfonyl group is added in order to reduce tissue accumulation and minimize adverse effects; is a class III antiarrhythmic agent with properties that inhibits sodium and potassium channels resulting in a prolongation of the action potential and refractory period in myocardial tissue. Inhibition of calcium and beta1- receptor blockade results in a decrease in AV conduction and sinus node function. However, dronedarone is less lipophilic than amiodarone, with a much shorter half-life [24 h] than amiodarone [several weeks]; it is also extensively metabolized primarily by the cytochrome P450 3A4 system and excreted in the bile with minimal renal excretion [67,68]. Dronedarone does not appear to cause any of the thyroid, pulmonary and neurological adverse effects observed with amiodarone [69,70].

Thyroid Hormones and Acute Cardiac Diseases

The studies on the long-term prognostic role of abnormal TSH value in adults with acute cardiac diseases are scarce. Recently, in a study of 1026 patients in patients with acute cardiac diseases it was documented that survival rate for cardiac death was lower in SHypo and in LTS than in euthyroid patients. Survival rate for overall death was lower in SHypo, SHyper and LTS than in euthyroid patients. After adjustment for several risk factors, the risk for cardiac death was higher in SHypo, in LTS, and in SHyper. The risk for overall death was higher in SHypo, in LTS and in SHyper than in euthyroid patients. In addition, the risk for SHypo, SHyper and LTS with respect to euthyroid patients, were proportional over the follow-up period [71,72].

In the same direction, another study evaluated the association between fT3 levels and the severity and prognosis of patients with AMI. A Total of 501 patients with AMI were enrolled. The patients were categorized into either the low fT3 group or the normal fT3 group according to the fT3 level on admission. All patients underwent a follow-up for 10±2 months for mortality from any cause and the occurrence of any MACEs. During the follow-up period, 33 patients died [6.6%] and the overall survival rates were 86% and 97.3% in patients with a low fT3 level and a normal fT3 level, respectively. The rates of MACEs were 66.7% and 45.5% in the patients with and those without low fT3 levels, respectively. The fT3 level was found to be the most important predictor of cumulative death and MACEs; and those patients with low fT3 levels had higher rates of MACEs and death [73].

Another study suggests that TH levels have predictive value when used to assess the extent of transmural infarction in patients with ST-Elevation Myocardial Infarction [STEMI]. A high T3 level was an independent predictor of transmural involvement after adjustment for the presence of Diabetes Mellitus and the use of glycoprotein IIb/IIIa inhibitors [74].

Another study investigated whether changes in TH in plasma are associated with early and late recovery of cardiac function in patients with Acute Myocardial Infarction [AMI]. A significant correlation between Left Ventricular Ejection Fraction [LVEF%] and T3 was found early after AMI [48h], whereas no correlation was observed between Creatinine Kinase-MB levels [CK-MB] and T3. Recovery of function [ΔEF%] was estimated as the difference of LVEF% between 48h and 6 months after AMI. A strong correlation was found between ΔEF% and total T3 at 6months after AMI; concluding that, changes in T3 levels in plasma are closely correlated with the early and late recovery of cardiac function after AMI; T3 levels at 6months appear to be an independent predictor of late functional recovery [75].

Intrinsic Effects of Amiodarone	Iodine-Induced Effects of Amiodarone
Direct thyroid cytoxicity	Iodine-mediated potentiation of thyroid autoimmunity
Blockade of TH entry into cells	Inability to escape from Wolf-Chaikoff effect
Inhibhition of type I and type II 5'-deiodinase	Unregulated hormone synthesis (Jod Basedow effect)
Decreased T3 binding to its TRs	Increased intrathyroid iodine stores

Table 6: Amiodarone and its effects on the thyroid gland.

Previously, a relationship between TH excess and the cardiac complications of angina pectoris and myocardial infarction was evaluated. A total of 1049 patients [aged 40 years or older] immediately on emergency medical admission were related to frequencies of angina pectoris and AMI as determined according to current diagnostic algorithms. After 3 years, those patients who had initially presented with angina pectoris or acute AMI were observed for subsequent coronary events; on hospital admission, the relative rate of angina pectoris and AMI was markedly high in patients with elevated serum free and total T3 levels. An initially elevated free T3 level was a risk factor for subsequent coronary events during the 3-year follow-up [76].

Conclusions

Thyroid hormones have important cardiovascular effects, the role of both excessive and insufficient thyroid hormones production in the pathogenesis of clinical cardiac diseases can be deduced from thyroid hormones-induced molecular changes. The molecular mechanisms of actions of thyroid hormones are genomic or non-genomic. Both the non-genomic and genomic effects of T3 act in concert to regulate cardiac function and cardiovascular hemodynamics. On the basis of the understanding of the cellular mechanisms of thyroid hormones action on the heart and cardiovascular system, it is possible to explain the changes in cardiac output, cardiac contractility, blood pressure, vascular resistance, and rhythm disturbances that result from thyroid dysfunction. It is well established that hyperthyroidism induces a hyperdynamic cardiovascular state, which is associated with a faster heart rate, enhanced left ventricular systolic and diastolic function, and increased prevalence of atrial fibrillation, whereas overt hypothyroidism is characterized by the opposite changes. Subclinical thyroid dysfunction is relatively common in patients over 65 years of age. In general, subclinical hypothyroidism increases the risk of CHD mortality and CHD events, but not of total mortality. The risk of CHD mortality and atrial fibrillation in subclinical hyperthyroidism is higher among patients with very low levels of thyrotropin.

Disclosure

The authors declare that there is no conflict of interest that could bias the impartiality of this review.

References

1. Fekete C, Lechan RM (2014) Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr Rev 35: 159-194.
2. Zhang J, Lazar MA (2000) The mechanism of action of thyroid hormones. Annu Rev Physiol 62: 439-466.
3. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR (2002) Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev 23: 38-89.
4. Orozco A, Valverde RC, Olvera A, García GC (2012) Iodothyronine deiodinases: a functional and evolutionary perspective. J Endocrinol 215: 207-219.
5. Dentice M, Marsili A, Zavacki A, Larsen PR, Salvatore D (2013) The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. Biochim Biophys Acta 1830: 3937-3945.
6. Olvera A, Mendoza A, Villalobos P, Mayorga-Martínez L, Orozco A, et al. (2015) The variable region of iodothyronine deiodinases directs their catalytic properties and subcellular localization. Mol Cell Endocrinol 402C: 107-112.
7. Lin JZ, Sieglaff DH, Yuan C, Su J, Arumanayagam AS, et al. (2013) Gene specific actions of thyroid hormone receptor subtypes. PLoS One 8: e52407.
8. Flamant F, Gauthier K (2013) Thyroid hormone receptors: the challenge of elucidating isotype-specific functions and cell-specific response. Biochim Biophys Acta 1830: 3900-3907.
9. Astapova I, Hollenberg AN (2013) The in vivo role of nuclear receptor corepressors in thyroid hormone action. Biochim Biophys Acta 1830: 3876-3881.
10. Lin HY, Tang HY, Davis FB, Mousa SA, Incerpi S, et al. (2012) Nongenomic regulation by thyroid hormone of plasma membrane ion and small molecule pumps. Discov Med 14: 199-206.
11. Bianco AC (2013) Cracking the code for thyroid hormone signaling. Trans Am Clin Climatol Assoc 124: 26-35.
12. Senese R, Cioffi F, de Lange P, Goglia F, Lanni A (2014) Thyroid: biological actions of 'nonclassical' thyroid hormones. J Endocrinol 221: R1-12.
13. Vargas-Uricoechea H, Sierra-Torres CH (2014) Thyroid hormones and the heart. Horm Mol Biol Clin Investig 18: 15-26.
14. Kahaly GJ, Dillmann WH (2005) Thyroid hormone action in the heart. Endocr Rev 26: 704-728.
15. Gerdes AM (2015) Restoration of thyroid hormone balance: a game changer in the treatment of heart failure? Am J Physiol Heart Circ Physiol 308: H1-10.
16. Chan YH, Tsai WC, Song Z, Ko CY, Qu Z, et al. (2015) Acute reversal of phospholamban inhibition facilitates the rhythmic whole-cell propagating calcium waves in isolated ventricular myocytes. J Mol Cell Cardiol 80: 126-135.
17. Biondi B, Palmieri EA, Lombardi G, Fazio S (2002) Effects of Thyroid Hormone on Cardiac Function: The Relative Importance of Heart Rate, Loading Conditions, and Myocardial Contractility in the Regulation of Cardiac Performance in Human Hyperthyroidism. JCEM 87: 968-974.
18. Grais IM, Sowers JR (2014) Thyroid and the heart. Am J Med 127: 691-698.
19. Sahay RK (2011) Thyrotoxicosis. J Assoc Physicians India 59 Suppl: 26-31.
20. Sabatino L, Iervasi G, Pingitore A (2014) Thyroid hormone and heart failure: from myocardial protection to systemic regulation. Expert Rev Cardiovasc Ther 12: 1227-1236.
21. Coceani M (2013) Heart disease in patients with thyroid dysfunction: hyperthyroidism, hypothyroidism and beyond. Anadolu Kardiyol Derg 13: 62-66.
22. Pearce EN, Yang Q, Benjamin EJ, Aragam J, Vasan RS (2010) Thyroid function and left ventricular structure and function in the Framingham Heart Study. Thyroid 20: 369-373.
23. Triggiani V, Iacoviello M (2013) Thyroid disorders in chronic heart failure: from prognostic set-up to therapeutic management. Endocr Metab Immune Disord Drug Targets 13: 22-37.
24. Koukoulis G, Polymeris A, Tzavara I, Pappas D, Thalassinos N, et al. (2002) Normalization of thyroid hormone levels in patients with either hyper- or hypothyroidism results in a profound change of atrial natriuretic peptide (ANP) levels. Hormones (Athens) 1: 104-112.
25. Galetta F, Franzoni F, Fallahi P, Tocchini L, Braccini L, et al. (2008) Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. Eur J Endocrinol 158: 85-90.
26. Faber J, Selmer C (2014) Cardiovascular disease and thyroid function. Front Horm Res 43: 45-56.
27. Dörr M, Wolff B, Robinson DM, John U, Lüdemann J, et al. (2005) The association of thyroid function with cardiac mass and left ventricular hypertrophy. J Clin Endocrinol Metab 90: 673-677.
28. Danzi S, Klein I (2003) Thyroid hormone and blood pressure regulation. Curr Hypertens Rep 5: 513-520.
29. Ozturk S, Alcelik A, Ozyasar M, Dikbas O, Ayhan S, et al. (2012) Evaluation of left ventricular systolic asynchrony in patients with subclinical hypothyroidism. Cardiol J 19: 374-380.
30. Zonstein J, Fein F, Sonnenblick E (1994) The heart and endocrine disease. In: Schlant R, Alexander R (eds) The heart, arteries and veins. (8thedn) McGraw-Hill, New York 1907-1921.
31. Yamanaka S, Kumon Y, Matsumura Y, Kamioka M, Takeuchi H, et al. (2010) Link between pericardial effusion and attenuation of QRS voltage in patients with hypothyroidism. Cardiology 116: 32-36.
32. Gao N, Zhang W, Zhang YZ, Yang Q, Chen SH (2013) Carotid intima-media thickness in patients with subclinical hypothyroidism: a meta-analysis. Atherosclerosis 227: 18-25.
33. Biondi B (2012) Mechanisms in endocrinology: Heart failure and thyroid dysfunction. Eur J Endocrinol 167: 609-618.
34. Galli E, Pingitore A, Iervasi G (2010) The role of thyroid hormone in the pathophysiology of heart failure: clinical evidence. Heart Fail Rev 15: 155-169.

35. Pingitore A, Iervasi G (2005) Thyroid (dys)function in heart failure: is it a potential target for medical treatment? Vasc Health Risk Manag 1: 97-100.

36. Schindhelm RK, ten Boekel E, Heima NE, van Schoor NM, Simsek S (2013) Thyroid hormones and erythrocyte indices in a cohort of euthyroid older subjects. Eur J Intern Med 24: 241-244.

37. Gopinathannair R, Sullivan R, Olshansky B (2009) Tachycardia-mediated cardiomyopathy: recognition and management. Curr Heart Fail Rep 6: 257-264.

38. Danzi S, Klein I (2014) Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am 43: 517-528.

39. Siu CW, Yeung CY, Lau CP, Kung AW, Tse HF (2007) Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart 93: 483-487.

40. Boccalandro C, Boccalandro F, Orlander P, Wei CF (2003) Severe reversible dilated cardiomyopathy and hyperthyroidism: case report and review of the literature. Endocr Pract 9: 140-146.

41. Rhee CM, Curhan GC, Alexander EK, Bhan I, Brunelli SM (2013) Subclinical hypothyroidism and survival: the effects of heart failure and race. J Clin Endocrinol Metab 98: 2326-2336.

42. Gerdes AM, Iervasi G (2010) Thyroid replacement therapy and heart failure. Circulation 122: 385-393.

43. Sabih DE, Inayatullah M (2013) Managing thyroid dysfunction in selected special situations. Thyroid Res 6: 2.

44. Triggiani V, Iacoviello M, Monzani F, Puzzovivo A, Guida P, et al. (2012) Incidence and prevalence of hypothyroidism in patients affected by chronic heart failure: role of amiodarone. Endocr Metab Immune Disord Drug Targets 12: 86-94.

45. Selmer C, Olesen JB, Hansen ML, Lindhardsen J, Olsen AM, et al. (2012) The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ 345: e7895.

46. Bielecka-Dabrowa A, Mikhailidis DP, Rysz J, Banach M (2009) The mechanisms of atrial fibrillation in hyperthyroidism. Thyroid Res 2: 4.

47. Bruere H, Fauchier L, Bernard Brunet A, Pierre B, Simeon E, et al. (2015) History of thyroid disorders in relation to clinical outcomes in atrial fibrillation. Am J Med 128: 30-37.

48. Traube E, Coplan NL (2011) Embolic risk in atrial fibrillation that arises from hyperthyroidism: review of the medical literature. Tex Heart Inst J 38: 225-228.

49. Ari H, Gürdogan M, Erdogan E, Ari S, Ata Y, et al. (2012) Short-term outcome of early electrical cardioversion for atrial fibrillation in hyperthyroid versus euthyroid patients. Cardiol J 19: 53-60.

50. TÄƒnase DM, Ionescu SD, Ouatu A, AmbÄƒruÅŸ V, Arsenescu-Georgescu C2 (2013) Risk assessment in the development of atrial fibrillation at patients with associate thyroid dysfunctions. Rev Med Chir Soc Med Nat Iasi 117: 623-629.

51. Zimmermann MB, Boelaert K (2015) Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol. 2015 Jan 12. pii: S2213-8587(14)70225-6. doi: 10.1016/S2213-8587(14)70225-6. [Epub ahead of print].

52. Kim EJ, Lyass A, Wang N, Massaro JM, Fox CS, et al. (2014) Relation of hypothyroidism and incident atrial fibrillation (from the Framingham Heart Study). Am Heart J 167: 123-126.

53. Franklyn JA (2013) The thyroid--too much and too little across the ages. The consequences of subclinical thyroid dysfunction. Clin Endocrinol (Oxf) 78: 1-8.

54. Biondi B (2012) Natural history, diagnosis and management of subclinical thyroid dysfunction. Best Pract Res Clin Endocrinol Metab 26: 431-446.

55. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, et al. (2010) Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 304: 1365-1374.

56. Rodondi N, Bauer DC (2013) Subclinical hypothyroidism and cardiovascular risk: how to end the controversy. J Clin Endocrinol Metab 98: 2267-2269.

57. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, et al. (2012) Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med 172: 799-809.

58. Gencer B, Collet TH, Virgini V, Auer R, Rodondi N (2013) Subclinical thyroid dysfunction and cardiovascular outcomes among prospective cohort studies. Endocr Metab Immune Disord Drug Targets 13: 4-12.

59. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jørgensen HL, et al. (2014) Duration of thyroid dysfunction correlates with all-cause mortality. the OPENTHYRO Register Cohort. PLoS One 9: e110437.

60. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, et al. (2014) Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab 99: 2372-2382.

61. Bogazzi F, Tomisti L, Bartalena L, Aghini-Lombardi F, Martino E (2012) Amiodarone and the thyroid: a 2012 update. J Endocrinol Invest 35: 340-348.

62. Cohen-Lehman J, Dahl P, Danzi S, Klein I (2010) Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol 6: 34-41.

63. Hudzik B, Zubelewicz-Szkodzinska B (2014) Amiodarone-related thyroid dysfunction. Intern Emerg Med 9: 829-839.

64. Leung AM, Braverman LE (2012) Iodine-induced thyroid dysfunction. Curr Opin Endocrinol Diabetes Obes 19: 414-419.

65. Eskes SA, Wiersinga WM (2009) Amiodarone and thyroid. Best Pract Res Clin Endocrinol Metab 23: 735-751.

66. Bogazzi F, Bartalena L, Martino E (2010) Approach to the patient with amiodarone-induced thyrotoxicosis. J Clin Endocrinol Metab 95: 2529-2535.

67. Palermo-Garófalo C, Martínez JH, Silva F, González E, Torres O, et al. (2013) The cardiology and endocrinology connection between amiodarone and thyrotoxicosis: case report and review of the literature. Bol Asoc Med P R 105: 47-53.

68. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, et al. (2010) A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol 21: 597-605.

69. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, et al. (2007) Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 357: 987-999.

70. Christiansen CB, Torp-Pedersen C, Køber L (2010) Efficacy and safety of dronedarone: a review of randomized trials. Expert Opin Drug Saf 9: 189-199.

71. Molinaro S, Iervasi G, Lorenzoni V, Coceani M, Landi P, et al. (2012) Persistence of mortality risk in patients with acute cardiac diseases and mild thyroid dysfunction. Am J Med Sci 343: 65-70.

72. Jabbar A, Razvi S (2014) Thyroid disease and vascular risk. Clin Med 14 Suppl 6: s29-32.

73. Zhang B, Peng W, Wang C, Li W, Xu Y (2012) A low fT3 level as a prognostic marker in patients with acute myocardial infarctions. Intern Med 51: 3009-3015.

74. Kim DH, Choi D-H, Kim H-W, Choi S-W, Kim B-B, et al. (2014) Prediction of infarct severity from triiodothyronine levels in patients with ST-elevation myocardial infarction. Korean J Intern Med 29: 454-465.

75. Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, et al. (2011) Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association? Eur J Endocrinol 165: 107-114.

76. Peters A, Ehlers M, Blank B, Exler D, Falk C, et al. (2000) Excess triiodothyronine as a risk factor of coronary events. Arch Intern Med 160: 1993-1999.