REVIEW ARTICLE

Thyrotoxic Heart Failure: A Narrative Review of Pathophysiology and Principle Management

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ABSTRACT

Heart failure is one of the most common causes of morbidity and mortality worldwide. Several studies showed that hyperthyroidism is a potentially reversible cause of heart failure and should be excluded in every heart failure patient, especially in the absence of a common cause of heart failure and structural heart disease. The diagnosis approach of thyrotoxic heart failure still remains a lack of specific guidelines. It is necessary to establish a thyroid dysfunction evidence accompanied by a structural and functional heart abnormality. Several studies have shown that cardiac dysfunction and heart failure, which related to hyperthyroidism, will be resolved in less than six months after a patient has reached euthyroid state. This narrative review summarizes the literature on the pathophysiology and principle management of thyrotoxic heart failure.

Keywords: Hyperthyroidism, Thyrotoxicosis, Heart failure

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INTRODUCTION

Heart failure is a clinical syndrome that has typical signs and symptoms. The syndrome will lead to decreased cardiac output or increased intra-cardiac pressure at rest or on exertion, so the heart is unable to pump blood as well as nutrition in a sufficient amount to meet the metabolic needs (1).

The incidence of heart failure is estimated at 1-3 per 1000 population at the age of 25 and increasing to 3-13% in the population over the age of 65 (2). A study looking at the prevalence of heart failure in Southeast Asia concluded that the prevalence of heart failure in Southeast Asian countries was higher compared to other countries around the world, with a prevalence rate of 6.7% in Malaysia and 4.5% in Singapore (3).

Thyroid hormone disorders are closely related to heart failure, either hypothyroid or hyperthyroidism. Hyperthyroidism can lead to abnormal cardiac contractility during arrhythmia, which is common in this condition. It is estimated 20% of patients with heart failure who are treated in the hospital have received treatment for thyroid hormone disorders and require a reevaluation of thyroid therapy during hospitalization (4). Another study conducted by Chung-Wah Siu et al. stated that the incidence of heart failure in hyperthyroid patients reached 5.8%. The study also revealed that the clinical symptoms of heart failure in hyperthyroid patients improved significantly three months after the patient was in the euthyroid stage (5).

This literature review attempt to summarize and evaluate existing data to discuss etiology, pathophysiology, consequences of hyperthyroidism on heart failure, and treatment of heart failure in hyperthyroidism patients. This review is expected to help clinicians to know the epidemiology, physiology, and relationship of heart failure with hyperthyroidism and ultimately get the appropriate management summary for these conditions, especially in critical situations, which are expected to play a role in reducing its morbidity and mortality.

PATHOPHYSIOLOGY

Thyroid Hormones Effects on the Cardiovascular Hemodynamic
The thyroid gland secretes two kinds of hormones, T3 (Triiodothyronine) and T4 (Thyroxine), in response to TSH (Thyroid Stimulating Hormone). The thyroid gland mainly secretes T4, which is converted into T3 in the liver, kidney, and skeletal muscle. The myocardium is mainly affected by T3 because there is no significant myocyte intracellular de-iodination activity. Thyroid

hormones will take effects on myocardium and vascular smooth muscle cells, which in turn cause hemodynamic changes. The effect of thyroid hormones at the cellular level is distinguished by their effects on heart muscle cells (myocytes) and vascular smooth muscle cells, as illustrated in figure 1 (6,7).
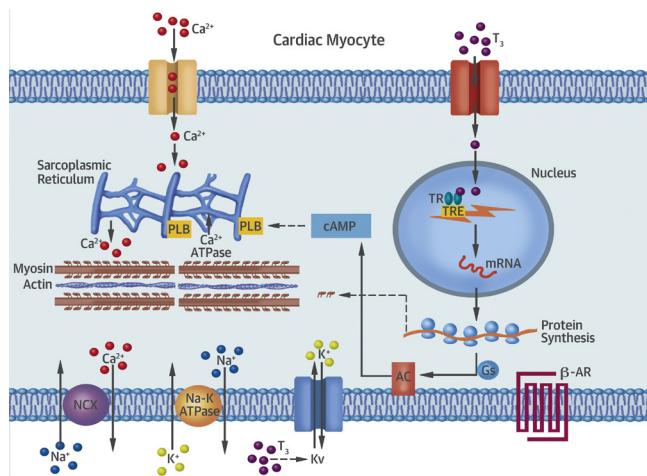
Figure 1: Cellular pathways and mechanisms of action of T3 on the cardiac myocyte. T3 has both genomic and nongenomic effects on the cardiac myocyte. Genomic mechanisms involve T3 binding to TRs, which regulate transcription of specific cardiac genes. Nongenomic mechanisms include direct modulation of membrane ion channels (14). AC: adenylyl cyclase; β-AR: β -adrenergic receptor; Ca²⁺-ATPase: sarcoplasmic reticulum calcium adenosine triphosphatase; cAMP: cyclic adenosine monophosphate; GS: stimulatory G (guanine nucleotide binding) protein; Kv: voltage-gated potassium ion channel; mRNA: messenger ribonucleic acid; Na-K ATPase: sodium-potassium adenosine triphosphatase; NCX: sodium calcium exchanger; PLB: phospholamban; T3: triiodothyronine; TR: thyroid hormone receptor; TRE: thyroid hormone response element.

Heart function and cardiovascular hemodynamic changes are mainly regulated through the genomic and non-genomic effects of thyroid hormones. Myocyte membrane has a transporter protein specifically for T3 and carries it into the cell nucleus. The genomic action of T3 at the cellular level is through its bond with T3 nuclear receptor (TR). This receptor mediates the induction of transcription of genes by binding with T3-Response-Element (TRE) in the promoter region of genes that are positively regulated by thyroid hormone (8). TRE is found in the promoter sequences of genes for α-myosin, Sarcoplasmic Reticulum Ca-ATPase (SERCA 2), and Na-K-ATPase, all three of which are regulators of the heart muscle. TR is a large family of steroid hormone receptors, but it is somewhat different because TR can bind to TRE either with or without ligand. The TR bond to TRE can be either as a monomer or homodimer, although it is more often as a heterodimer with 1 of 3 retinoid X receptor isoforms (RXRα, RXRβ, RXRγ). TR will induce gene transcription if it binds to T3, but if there is no T3, it will repress the transcription process (4,9).

Thyroid hormones have a significant effect on the function and structure of the heart. Hyperthyroid conditions will affect cardiovascular hemodynamic and result in high output heart failure. In the later stages, this condition will result in dilated cardiomyopathy. Hemodynamic changes in hyperthyroidism occur due to a decrease in systemic vascular resistance and increased heart rate, myocardial contractility, and blood volume. Thyroid hormones can reduce systemic vascular resistance (SVR) through their direct effects on the vascular smooth muscle cells (VSM) and vascular endothelial cells through nitric oxide synthesis and ion canal activity (10). The synthesis of nitric oxide in endothelial cells will act paracrine in the surrounding smooth muscle cells causing vascular relaxation. In hyperthyroidism, systemic vascular resistance decreases while blood volume and perfusion in peripheral tissues increase. Reduced SVR will cause a decrease in the mean arterial pressure, which in turn activates the Renin-Angiotensin-Aldosterone (RAA) system so that sodium absorption in the kidneys will increase. T3 also increases the production of erythropoietin, which will cause an increase in the number of red blood cells. These changes will cause an increase in blood volume and preload in patients with hyperthyroidism. Increased cardiac output in hyperthyroidism can reach 50% to 300% of normal individuals (11).

Thyroid Hormones Effect on the Myocardium
The effects of thyroid hormones on cardiac myocytes can be achieved by regulating the expression of major regulatory and structural genes from several enzymes of various structural and functional proteins such as MHC α and β, SERCA 2 and their inhibitors (i.e., phospholamban), potassium channels, β1 adrenergic receptors, guanine nucleotide regulating protein, adenylate cyclase, Na/K-ATPase, and Na/Ca transporter. The overall effect is the influence of thyroid hormones, both directly and indirectly, on systolic and diastolic functions (9,12).

The heart muscle moves involuntarily and consists of myofibril. This myofibril consists of a combination of thick and thin filaments, and each unit is called a sarcomere. The thin filament consists of actin, and thick filament consists of myosin. Contraction occurs when both filaments move and shift together. The thick chain myosin gene encodes two contractile protein isoforms from thick filaments in myocytes. The direct effect of thyroid hormones on contractility achieved through an increase in MHC-α expression (which has high contractility) and decreased expression of MHC-β (which is associated with efficient and effective energy use). SERCA 2 and its inhibitors (phospholamban) regulate intracellular calcium cycle. Increased ventricular relaxation is mediated through activation of SERCA 2, which has a clinical impact by reducing cytosolic Ca at the end of diastole. Increased ventricular contraction and relaxation function are also affected by

both β-adrenergic and Na / K ATPase receptors, which regulated by T3 (9).

Thyroid hormones also have extra-nuclear non-genomic effects on cardiac myocytes (in the cytoskeleton, plasma membrane, sarcoplasmic reticulum, endoplasmic reticulum, cytoplasm, and mitochondria) and systemic blood vessels. This non-genomic T3 effect occurs quickly and does not involve the transcription process mediated by TRE. This T3 effect includes changes in various membrane ion channels (canal Na, K, Ca) effects on actin polymeration, function, and gene expression in mitochondria and various intracellular signal pathways in the heart and vascular smooth muscle cells like calcium-dependent cyclic AMP signal cascade or a cascade of protein kinase signals. In an in vitro trial, the direct effect of T3 on vascular evidence was non-genomic and endothelial independent, but in different in vivo trials, different results were found in the correlation between T3-induced dilatation and NOS activation. T3 also has several genomic effects on vascular by modulating the expression of vital genes to maintain endothelial homeostasis, such as angiotensin receptors in vascular smooth muscle cells (7,11).

Myocardial perfusion was also affected by thyroid hormones and the interaction of their receptors. T3 can produce a vasodilatory effect within hours after administration to patients undergoing coronary artery bypass grafting (13,14) by regulating endothelial nitric oxide production and vascular tone (14,15). This effect is associated with the induction of phosphatidylinositol 3-kinase/protein (PI3K/Akt) signaling pathway (16,17). Furthermore, thyroid hormone stimulates arteriolar growth in the normal heart and after myocardial infarction suggesting its proangiogenic effect. This proangiogenic effect is mediated by increased transcription of proangiogenic genes and expression of hypoxic inducible factor-1α (HIF-1α) and mediated by activation of integrin αVβ3 (17–19).

Thyroid hormones accelerate the systolic and diastolic depolarization, reduce the action potential and refractory period of atrial and atrioventricular myocytes, thus affecting the pacemaker and conductive cardiac system (20,21). The difference between atrial and ventricular sensitivity to thyroid hormones (mainly affected by beta-adrenoreceptors density) may be the cause of atrial and ventricular arrhythmias variation (21). Atrial cardiomyocytes have twice as high as beta-adrenoreceptors in the LV, thus affect the atrial sensitivity to arrhythmogenic thyroid hormone effects (22). Furthermore, thyroid hormones also shortened the action potential by regulating the intracellular level and distribution of ion channels in cell membrane. Its effect due to regulation of some myocardial genes that encode synthesis of ion channels by thyroid hormones (21,22). The effects of thyroid hormones on the hemodynamic of the heart and vascular systems include a decrease in systemic vascular resistance, increased heart rate at rest, increased left ventricular contractility, and increased blood volume. Hyperthyroid causes changes in all β adrenergic receptor complexes in cell membranes, but overall cardiac sensitivity to adrenergic stimuli is still normal. Administration of β adrenergic receptor antagonists reduce the heart rate but does not change systolic strength; this suggests that T3 has a direct effect on myocytes (23).

CARDIOVASCULAR MANIFESTATION IN HYPERTHYROIDISM

The classic syndromes of hyperthyroidism patients include irritability, insomnia, anxiety, sweating, hunger, muscle weakness, frequent bowel movements, decreased libido, and tremors of the fingers (24).

Hyperthyroidism patients also have various symptoms and signs related to the typical cardiovascular system such as palpitations, tachycardia, severe activity intolerance, widening pulse pressure (increased systolic pressure, decreased diastolic pressure) and sometimes pulsus deficits and irregular heartbeat. On physical examination, it can be seen hyperdynamic precordial, increased pulse pressure, increase in first heart sound, increased pulmonary component of second heart sound, and third heart sound. Cardiac output can increase by 50-300% compared to normal people as a result of a combination of increased resting heart frequency, contractility, ejection fraction, blood volume, and decreased systemic vascular resistance (9).

Exercise intolerance in hyperthyroid patients can be caused by an inability to increase the heart rate or to lower SVR in response to exercise. Exercise intolerance can also be caused by skeletal respiratory muscle weakness in the elderly or those who have a long history of hyperthyroidism. Although rare, in some cases, hyperthyroid patients can present with a major complaint of chest pain during treatment, along with electrocardiography changes that reflect cardiac ischemia. Patients with hyperthyroidism can show signs and symptoms of heart failure, in spite of contractility and cardiac output increase. The old literature shows this as high-output heart failure (Figure 2) (25).

Some patients with prolonged hyperthyroidism accompanied by sinus tachycardia or atrial fibrillation can end up with left ventricular dysfunction associated with rapid ventricular rate because they are no longer able to increase heart rate and decrease SVR during activity. The presence of ischemic heart disease and previous hypertensive heart disease can also predispose hyperthyroid patients to heart failure. If the patient has heart failure with left ventricular systolic dysfunction, we will get various classic signs and symptoms of heart failure due to low cardiac output, congestion, or enlargement of the heart itself (9).
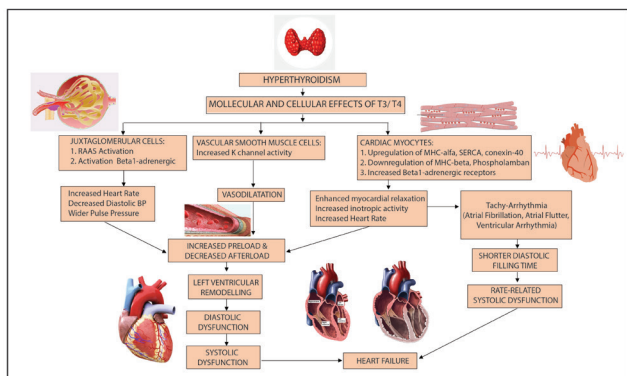
Figure 2: Effects of thyroid hormones on cardiovascular hemodynamic and its progression to heart failure. BP: blood pressure; MHC: myosin heavy chain; RAAS: renin–angiotensin–aldosterone system; SERCA: sarco/endoplasmic reticulum Ca²⁺-ATPase.

Thyroid hormones have beneficial effect on cardiovascular system. Some review have shown that short-term hyperthyroidism may improve left ventricle (LV) systolic function and enhancing LV diastolic function (14,26). However, untreated long-standing hyperthyroidism is associated with reduced cardiovascular and respiratory reserve during exercise despite the high cardiac output state (14,27). This long-standing untreated hyperthyroidism increased risk of major cardiovascular event up to 16%, mainly due to higher heart failure incidence (as shown in figure 3) even in patients without underlying heart disease (14,28).
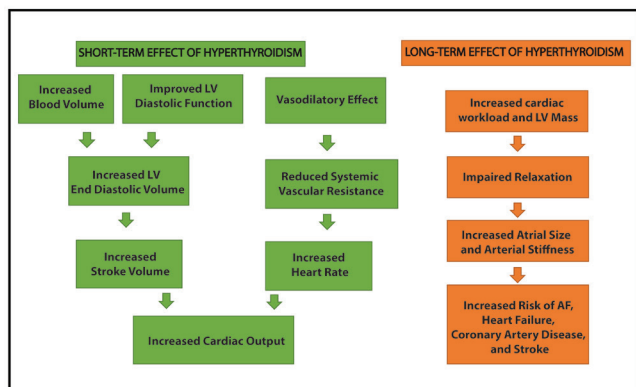
Figure 3: Mechanistic effect of hyperthyroidism duration on the progression of heart failure (14). AF: atrial fibrillation; CHD: coronary heart disease; HF: heart failure; LVEDV: left ventricular end-diastolic volume; LVM: left ventricular mass; SVR: systemic vascular resistance.

Heart failure in patients with thyrotoxicosis is progressive and may be defined into three stages: (a) hyperkinetic, characterized by preserved LV function, but at physical load LV ejection fraction does not increase; (b) normokinetic, which is a compensatory stage characterized by reversible myocardial hypertrophy and preserved cardiac output; and (c) hypokinetic stage, which is a decompensation stage characterized by low cardiac output and stroke volume with reversible or irreversible heart chamber hypertrophy and dilatation

(21,22).

HEART FAILURE DIAGNOSIS IN HYPERTHYROIDISM

It is necessary to establish a thyroid dysfunction evidence accompanied by a structural and functional heart abnormality. Evaluation of thyroid function can be done by examining levels of FT3, FT4, TSHs, thyroid antibodies, radioisotope scans, thyroid ultrasound, and fine needle biopsies if needed. Evaluation of structural and functional heart disorders can be done by examining chest x-rays, electrocardiography, and echocardiography (5).

Thyroid Function Test
Serum TSH measurement should be used as the first-line screening test for thyroid dysfunction (both hypothyroid and hyperthyroidism). This measurement is the most sensitive and specific among other blood tests used in evaluation of suspected hyperthyroidism. However, several conditions such as drugs or acute illness will alter TSH level, so some clinicians suggest to assess both TSH and free T4 to improve the diagnostic accuracy (29).
Measuring T3 might also play an important role. In heart failure patients, low T3 levels have been linked with myocardial fibrosis and disorders in myocardial perfusion and metabolism (30). The low T3 syndrome, defined as a low T3 level with normal levels of TSH and FT4, is present in 14% to 30% of heart failure patients (31–33). In previous studies of hospitalized heart failure patients, low T3 syndrome was independently associated with higher all-cause mortality (32,34). A study by Kannan et al. also showed that low T3 were poor prognostic indicators in ambulatory patients with heart failure (32).

Echocardiography
Echocardiography is the most useful and commonly available tool to determine a diagnosis in patients with suspected heart failure. Echocardiography provides immediate information about heart chambers size, ventricular systolic and diastolic function, wall thickness, valve function, and pulmonary hypertension (35). This information is very important in making a diagnosis and in determining the right treatment (1,35).

MANAGEMENT OF HEART FAILURE IN HYPERTHYROIDISM

Management of heart failure in hyperthyroidism consists of relieving the clinical manifestations of heart failure and restore hyperthyroid state to euthyroid as the underlying condition. Treatment of hyperthyroidism consists of 3 common strategies with antithyroid drugs, thyroidectomy or administration of radioactive iodine. The management of heart failure is differentiated based on impaired left ventricular systolic and diastolic function, presence or absence of congestive syndrome, presence or absence of rhythm disturbances, and

accompanying complications such as shock and cardiac tamponade (24,36).

Management of Hyperthyroidism
Several studies have shown that cardiac dysfunction and heart failure that occurred before will resolve in less than six months after a patient has reached a euthyroid state. A study by Smit et al., showed that prolonged subclinical hyperthyroidism with diastolic dysfunction would be resolved after achieving euthyroid (5,37). A recent study by Ruiz et al. showed that patients with long duration of disease had worse myocardial damage characterized by left ventricular dysfunction, increased left ventricular end-diastolic size, and decreased left ventricular ejection fraction. The study also shows that resolution of cardiac function is more common in male patients than women. Not improving cardiac function can be associated not only with high thyroid hormone levels but also due to changes in the sympathetic system, which can simultaneously cause tachy-cardiomyopathy. Antithyroid therapy and beta-blockers to control the heart rate, prevent heart remodeling, and avoid hemodynamic overload provide cardiac improvement and resolution in heart failure patients triggered by hyperthyroidism (38).

Management of Heart Failure
The management of congestive heart failure with impaired systolic function patients includes restriction of salt and fluids consumptions, administration of diuretics, vasodilators, RAAS antagonists, and beta-blockers (Table I) (1,39).

Table I: Beta-adrenergic receptor blockade in the treatment of thyro-toxicosis and heart failure (15).

Drug	Dosage	Frequen-cy	Considerations
Esmolol	50-100 μg/kg/min iv		Commonly used in severe thyro-toxicosis
Atenolol	25 mg; titrated up to 100 mg	1-2 times per day	Selectively block β-1 adrenergic; should be avoided in pregnant patients
Metoprolol	25 mg; titrated up to 50 mg	2-3 times per day	Relative β-1 adrenergic block-ade
Propanolol	10 mg; titrate up to 40 mg	3-4 times per day	Non-selective β blocker which preferred for nursing and preg-nant patients; at high dose, it will block T4 to T3 conversion

Left ventricular dysfunction associaed with ventricular rate in hyperthyroidism will improve with the administration of beta-blockers. Beta blocking therapy is the first choice to reduce heart rate in thyrotoxicosis patients. Digitalis and diuretics can be given to patients with severe heart failure with pulmonary edema. Both drugs are also safe and effective when administered together with beta-adrenergic inhibitors (1). Digitalis is not recommended to treat atrial fibrillation in hyperthyroidism because the effect is difficult to be predicted since its clearance increased in hyperthyroidism, so a larger dose is needed (40). Therapy with calcium blockers should be avoided because it will further potentiate the reduction of blood pressure through its effects on arteriole smooth muscle cells, causing cardiovascular shock and acute hypotension. Calcium inhibitors can be used with caution in those who cannot receive beta-blockers (11).

CONCLUSION

Hyperthyroidism affects cardiovascular hemodynamic and leads to high-output heart failure. However, in patients with both severe and chronic hyperthyroidism, left ventricular dysfunction and heart failure are commonly related to tachyarrhythmia conditions. The management of hyperthyroidism should be the first procedure carried out in hyperthyroid patients with heart failure.

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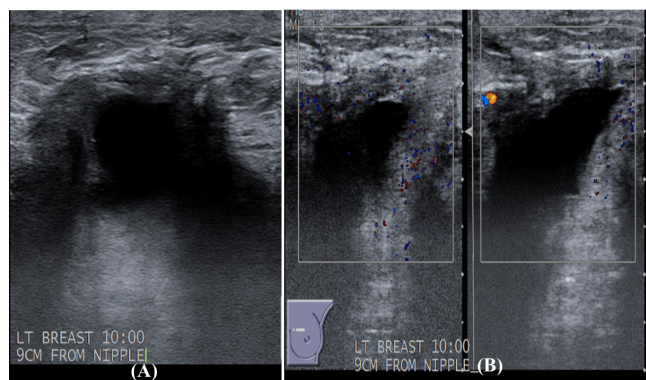
Figure 4: (A) Axial view and (B) Colour Doppler - example for false-positive case. Ultrasound images showed irregular, hypoechoiec lesion with posterior shadowing and thick wall at left breast 10 OC, adjacent to scar tissue (post wide local excision for previous left invasive ductal carcinoma). BI-RADS 5 was given and biopsy performed with HPE turn out to be breast abscess secondary to chronic granulomatous mastitis.

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