# THYROTOXICOSIS AND THE HEART – A REVIEW OF THE LITERATURE

AO Ogbera

Correspondence:
Ogbera AO
Department of Medicine,
Lagos State University Teaching Hospital (LASUTH),
Ikeja. Lagos, Nigeria
Email: oogbera@yahoo.co.uk

**Thyrotoxicosis and the heart.**

**Abstract**:
Thyrotoxicosis is a common endocrine disorder affecting more females than males. It is well known that one of the main complications of thyrotoxicosis is heart disease, including heart rhythm abnormalities. Studies have clearly shown that patients with hyperthyroidism are more likely to die from heart disease or stroke, despite effective treatment. This article sets out to review the range of possible cardiovascular complications that occur in thyrotoxicosis as well as the pathophysiological mechanisms responsible for these complications. Management of these complications is also discussed.

**Introduction**

The term thyrotoxicosis refers to the hypermetabolic clinical syndrome resulting from serum elevations in thyroid hormone levels, specifically free thyroxine (T4), and triiodothyronine (T3), or both. Although hyperthyroidism is the commonest cause of thyrotoxicosis, this condition may also be caused by inflammation of the thyroid gland, which causes release of stored thyroid hormone but not accelerated synthesis and ingestion of exogenous thyroid hormone[1-2]. The manifestations of thyrotoxicosis may be multi-systemic and clinical features range from silent to florid[3]. Thyrotoxicosis may be associated with cardiovascular complications[4-5] which often lead to increased morbidity and mortality in this group of people. Reported prevalence rates of thyrocardiac disease range from 7.4%-22%[6-8.]

The cardiac manifestations of thyrotoxicosis which were described as far back as at the original description of thyrotoxicosis by Parry and Grave[9] have long been recognized to be among the earliest and most consistent phenomenon of this disorder. Caleb Hillier Parry's classic description of a woman whom he saw in 1786 with goiter and palpitations, whose "each systole shook the whole thorax," first suggested to him "the notion of some connection between the malady of the heart and the bronchocoele (goiter)[10]. The association of thyrotoxicosis and cardiovascular morbidity is well established. The cardiovascular system has been found to be very sensitive to the effects of thyroid hormone excess. There are several

cardiac manifestations of thyrotoxicosis, including enlargement of the heart, atrial fibrillation, high output heart failure, hypertrophic cardiomyopathy, anginal syndrome without evidence of coronary artery disease, systolic hypertension and sudden death. The common cardiovascular manifestations of thyrotoxicosis include tachyarrhythmias, associated thrombo-embolism, and heart failure[11]. Other notable tacchyarrythmias which may occur albeit infrequently are paroxysmal atrial tachycardia and atrial flutter. Intra-atrial conduction disturbances and ventricular premature beats have also been documented[12-13].

**Thyrotoxicosis and Arrhythmias**

Thyrotoxicosis is associated with arrhythmias, which are disturbances in the heart's normal rhythm and tachycardia, which causes a rapid heart rate. Sinus tachycardia which is a common feature of thyrotoxicosis is a known cause of palpitations in people with this disorder. It is the commonest electrocardiographic feature of thyrotoxicosis occurring usually in more than 50% of people with thyrotoxicosis[9]. The heart rate in hyperthyroidism is rapid both during the day and during sleep. Atrial premature depolarizations, paroxysmal atrial tachycardia, atrial flutter and, most significantly, atrial fibrillation all occurs in hyperthyroidism.

Atrial fibrillation is the most common cardiac complication of thyrotoxicosis and it is associated with a higher risk of thromboembolism that often involves the central nervous system[10]. The incidence of atrial fibrillation ranges from about 10–21% in unselected patients[14-15], compared with 0.4%- in the overall adult population[16-17]. Prevalence rates of 17% have been reported by some African series[8,15,18]Atrial fibrillation has been found to occur more commonly in males with thyrotoxicosis[19] even though thyrotoxicosis is five to six times commoner in females than in males[18]. Increasing age, and associated rheumatic or hypertensive heart disease are some of the other factors that have been found to be significantly associated with the presence of atrial fibrillation in people with thyrotoxicosis[20-21.] Reports have shown an association between subclinical hyperthyroidism and development of atrial fibrillation though available data do not support the hypothesis that unrecognized subclinical hyperthyroidism or subclinical hypothyroidism is associated with other cardiovascular disorders or mortality[22] Ventricular arrhythmias are not usually attributable to hyperthyroidism alone and their presence is a strong presumptive evidence of intrinsic cardiac disease[10]. Intra-

atrial conduction disturbances manifesting as prolongation or notching of the *P*-wave, and prolongation of the PR interval, have been documented in thyrotoxicosis and in the absence of treatment with digitalis[12]. An unusual case of bradycardia in thyrotoxicosis which was later followed by tachycardia and subsequent reversal to sinus rhythm following treatment was documented by Yang et al[23]. Second or third degree heart block complicating hyperthyroidism is rare, and has most commonly been reported in association with acute inflammatory disease, hypercalcaemia, administration of drugs (for example digoxin), or co-existing heart disease[24].

**Thyrotoxicosis and Thromboembolism**

The incidence of thromboembolism in thyrotoxicosis is considerable as up to 3 to 10% of all thyrotoxic patients may have systemic emboli[25]. Reported prevalence rates of thromboembolism in thyrotoxic patients with atrial fibrillation range from to 30-40%[14,25] and cerebral emboli usually account for about half of these episodes. Thromboembolism may be due to an underlying procoaguable state in hyperthyroidism[26] or other factors such as the increased incidence of mitral valve disease[27]. Mitral valve regurgitation is a common feature of thyrotoxic heart disease whereas mitral valve prolapse is a rarity in this group of people in which it is associated with aging[28-29].

**Thyrotoxicosis and systemic hypertension**

Hypertension occurs in about a third of subjects with thyrotoxicosis. People with thyrotoxicosis have hyperdynamic hypertension and high cardiac output, seen predominantly as elevated systolic blood pressure[30]. Systolic hypertension has been suggested to be due to the inability of the vasculature to accommodate the increase in cardiac output and stroke volume, a mechanism that explains the infrequent presence of diastolic hypertension[31].

**Thyrotoxicosis and Cardiomyopathy**

Some authors have proposed that there is a specific thyrotoxic cardiomyopathy, with reduced myocardial function in the hyperthyroid state, reversible after treatment[32-33]. However, this is not supported by data from invasive monitoring studies which have demonstrated increased myocardial contractility and cardiac index at rest in patients with hyperthyroidism whether

symptoms of cardiac failure were present or not[34-35]. The form of cardiomyopathy that is commonly reported in thyrotoxicosis is dilated cardiomyopathy[36-37]. Cardiomyopathy may present with diastolic or systolic dysfunction. It is a potentially reversible cause of cardiomyopathy. Thus it is advisable that hyperthyroidism be excluded in every new patient, young and old presenting with cardiomyopathy especially in the absence of coronary artery disease[38]. In a few instances, cardiomyopathy becomes irreversible after a prolonged period of successful treatment of thyrotoxicosis[39-40]. It is however debatable whether the underlying pathophysiologic mechanism for the development of cardiomyopathy is due to tachycardiomyopathy or to thyrotoxic cardiomyopathy[39]. There are usually no specific abnormalities in myocardial biopsy specimens taken from these patients[39].

**Thyrotoxicosis and Heart failure**

Overt heart failure in hyperthyroidism occurs in 6–19% of unselected patients, the incidence increasing with age[41-42]. The hemodynamic features of hyperthyroidism are due to functional alterations in both the peripheral circulation and the myocardium. There is an increase in total blood volume and a decrease in systemic vascular resistance[43]. These effects increase preload and decrease afterload and are accompanied by an increase in heart rate[35]. The result is a high output cardiac state. One notable key risk factor leading to the development of cardiac failure in thyrotoxicosis is atrial fibrillation in which the underlying pathophysiological mechanism is the presence of a rapid ventricular response and loss of the atrial kick which impair diastolic filling. Other less common causes include the failure of mitral valve leaflet apposition and consequent mitral regurgitation secondary to left ventricular dilatation[11]. There is a fundamental impaired contractility as is also present in other forms of high output heart failure[11].

**Pathophysiology of the hyperdynamic cardiocirculatory state in hyperthyroidism.**

A number of studies have suggested that the combined effects of thyroid hormone on certain molecular pathways on the heart and vasculature, at both the genomic and nongenomic level are responsible for the hyperdynamic state in thyrotoxicosis[4]. In thyrotoxicosis, there is an increase in chronotropism and ionotropism probably caused by unbalanced sympathovagal tone due to a relative rather than an absolute adrenergic overdrive[44-45].Thyroid hormone has a

consistent positive chronotropic effect, and resting sinus tachycardia is the most common cardiovascular sign of human hyperthyroidism[45]. It has been suggested that thyroid hormone may directly affect sinoatrial node firing[46-47].

Preload which is the hemodynamic force exerted on the ventricular wall during filling plays a major role in the regulation of the stroke volume of the heart (Frank-Starling mechanism). It is one of the most efficient mechanism by which cardiac output adjusts to the peripheral metabolic demand. In the intact organism, preload is largely regulated by venous return, which, in turn, depends on systemic vascular resistance and venous tone. It has been demonstrated that blood volume is increased in hyperthyroid patients and this is in support of the hypothesis that preload has a mandatory role in determining the high output state[48-49]. Similarly, some researchers have demonstrated that the renin-angiotensin-aldosterone system is activated in hyperthyroid patients[50]. Thyroid hormone has been shown to up-regulate erythropoietin secretion and, in turn, red blood cell mass, which may also contribute to the increase in total blood volume and cardiac preload[51-53]. Further evidence for increased preload in hyperthyroidism is provided by the consistent increase in indices of early left ventricular (LV) filling, and by the faster LV relaxation independent of the effect of heart rate and catecholamines[54].

Ventricular afterload, the hemodynamic force exerted on the ventricular wall during ejection which is a determinant of the stroke volume of the heart has been found to be reduced in hyperthyroid patients[54-56]. This is due to the finding that thyroid hormone directly promotes arterial smooth muscle relaxation[57-59], so leading to a reduction in systemic vascular resistance both acutely and chronically[47-48.] Myocardial contractility is not increased in hyperthyroidism, rather, the high output state is probably due to the synergistic interaction between the increase in heart rate and ventricular preload. The augmented cardiac performance accompanying human hyperthyroidism seems to be mostly an adaptive response to changes in peripheral hemodynamics rather than the result of a mandatory enhancement of myocardial contractility. This is sequel to an increase in the peripheral metabolic demand promoted by thyroid hormone[60]. Therefore, it seems that the effects of thyroid hormone on peripheral circulation play a central role in regulating cardiac performance. By reducing systemic vascular resistance, thyroid hormones shift blood from the arterial to the venous compartment of the vascular

system, thus unloading the arterial tree. This effect, coupled with activation of the renin-angiotensin-aldosterone system and with increased red blood cell mass, increases blood volume and, in turn, the venous return to the heart.

**Pathophysiology of heart block in thyrotoxicosis**

Postulated mechanisms for complete heart block in thyrotoxicosis include interstitial inflammation of the atrioventricular (AV) node, the His-bundle and its branches[61]. Necropsies in patients with fatal hyperthyroidism have revealed dilated ventricles, myocyte hypertrophy, edema, interstitial and perivascular fibrosis, cellular infiltration and myocyte necrosis[62], which could also affect the conducting system within the heart to generate varying and intermittent degrees of heart block. Focal myocarditis affecting the region around the AV node has also been postulated to result in heart block[63]. Repeated inflammation of the cardiac conducting system (especially the AV node) is another reason for cumulative damage, leading ultimately to complete heart block.

**Management of thyrotoxic heart disease**

Hyperthyroidism results in excess mortality from increased incidence of circulatory diseases and dysrhythmias. Treatment of hyperthyroidism results in conversion to sinus rhythm in up to two-third of patients[64]. ßeta-Adrenoceptor blockers are widely used in the management of patients with thyrotoxicosis, typically in short-term management before euthyroidism is achieved. This group of drugs has a well-established role in the management of symptoms, including palpitation[65]. Beta-blockers in addition to reducing left ventricular hypertrophy also reduce atrial and ventricular arrhythmias in patients with hyperthyroidism[64]. ßeta-Adrenoceptor blockers are the drugs of choice in the absence of decompensated congestive heart failure. They are however used in high doses because of increased clearance in thyrotoxic states. Heart failure in the presence of thyrotoxicosis, especially in the elderly, may pose a problem in management because of its heterogeneity. Albeit, there may be an underlying cardiovascular disorder and tachyarrhythmias. Though correction of underlying thyrotoxicosis is the primary concern in management, of paramount significance, is rapid correction of symptoms[66]. Treatment of heart failure should aim at reduction of volume overload by the usage of

diuretics. Reduction of ventricular response rate can be achieved in those with associated atrial fibrillation through the use of digoxin but in higher than usual doses. This is a resultant effect of increased renal clearance of digoxin and increase in Na/K ATPase units in the cardiac muscles of people with this disorder[66].

Beta blockers may be used cautiously in thyrotoxic heart failure if tachycardia deemed to be a critical feature of heart failure.

The increased risk of thromboembolic phenomena in people with thyrotoxic heart disease especially in the presence of atrial fibrillation may warrant the initiation of anticoagulant therapy[67]. The use of anticoagulant therapy should be individualized and dependent on factors such as age, underlying cardiovascular disease, hypertension and independent risk factors for thromboembolism. Anticoagulation could be in the form of initial heparinization followed by institution of warfarin or warfarin treatment solely. The maintenance dose of warfarin should be reduced because of increased clearance of Vitamin K dependent factors in thyrotoxicosis[68]. Aspirin may be offered to those not offered anticoagulation therapy[67].

**Conclusion**

The cardiovascular complications which are often a cause of morbidity and mortality in thyrotoxicosis are fairly consistent features of this disorder. An understanding of the basic underlying pathophysiologic mechanisms, clinical features and management is a step in the right direction towards reducing fatal complications of this all important endocrine disorder.

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