# Thyroid Dysfunction and Arrhythmias

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**Abstract**

Context: Arrhythmia is a major cause of morbidity and mortality in Europe and in the United States. The aim of this review article was to assess the results of the prospective studies that evaluated the risk of arrhythmia in patients with overt and subclinical thyroid disease and discuss the management of this arrhythmia.

Evidence Acquisition: Reports published with the following search terms were searched: thyroid, hypothyroidism, hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, levothyroxine, triiodothyronine, antithyroid drugs, radioiodine, deiodinases, atrial flutter, supraventricular arrhythmia, ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation, torsade de pointe, amiodarone and atrial fibrillation. The investigation was restricted to reports published in English.

Evidence Synthesis: The outcome of this analysis suggests that patients with untreated overt thyroid dysfunction are at increased risk of arrhythmia.

Conclusions: The timely recognition and effective treatment of thyroid dysfunction in patients with arrhythmia is mandatory because the long-term and prognosis of arrythmias may be improved with the appropriate treatment of thyroid dysfunction.

## Abbreviations

| | |
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| AF | Atrial fibrillation |
| AIT | Amiodarone-induced thyrotoxicosis |
| AP | Action potential |
| EAD | Early afterdepolarization |
| ECG | Electrocardiogram |
| FT4 | Free thyroxine |
| *I*K | Delayed rectifier potassium current |

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|---|---|
| LQTS | Long QT syndrome |
| PLB | Phospholamban |
| PVs | Pulmonary veins |
| SERCA2 | Calcium-activated adenosine triphosphatase |
| SR | Sarcoplasmic reticulum |
| SR $Ca^{2+}$-ATPase | Sarcoplasmic reticulum calcium pumps |
| T3 | Triiodothyronine |
| TdP | Torsade de pointes |
| TH | Thyroid hormone |
| TSH | Thyroid stimuling hormone |
| UFH | Unfractionated heparin |
| VF | Ventricular fibrillation |
| VPB | Ventricular premature beats |
| VT | Ventricular tachycardia |

## Introduction

The most common clinical manifestations of thyrotoxic heart disease are heart rate disorders, in particular, sinus tachycardia and atrial fibrillation, which presents in 28 % of patients [1]. Typical arrhythmias found in hyperthyroidism are atrial premature contractions or atrial fibrillation, the latter occurring in 9–22 % of patients [2]. Conversely, ventricular premature contractions are rare in this setting, and if present, their frequency is not decreased after treatment [3]. Malignant ventricular arrhythmias such as ventricular tachycardia or fibrillation, which are potentially fatal, are exceptional [4] and usually occur only in patients with marked heart failure or associated cardiac disease [5]. Surprisingly, there have been few population-based studies examining the long-term influence of thyroid disease and its treatment on morbidity and mortality [6].

## Genomic Action of Thyroid Hormone on Heart

Thyroid hormone exerts a broad range of effects on development, growth, and metabolism. The clinical manifestations of thyroid hormone excess and deficiency are dramatic examples of the myriad actions of the hormone. Thyroxine ($T_4$), the primary secretory product of the thyroid, is relatively inactive and is converted to the active hormone, triiodothyronine ($T_3$), by the enzyme thyroxine 5′-deiodinase. The actions of thyroid hormone are primarily the result of the interaction of $T_3$ with nuclear receptors for $T_3$ that bind to regulatory regions of genes (thyroid hormone-response elements) and modify their expression [7]. These receptors have been cloned, and there has been considerable progress in unraveling the various mechanisms by which thyroid hormone regulates gene expression [8].

The clinical findings in hypothyroidism and hyperthyroidism are the net result of the actions of products of a variety of genes whose expression is directly or indirectly regulated by $T_3$. There are markers of thyroid hormone action that can be monitored clinically and that provide information about the ability of $T_3$ to regulate a gene product. Thyroid hormone excess reduces systemic vascular resistance, enhances cardiac contractility, and has a positive chronotropic effect [9]. Thyroid hormone deficiency has the opposite effects: it increases systemic vascular resistance, decreases contractility, and slows the heart rate. These changes in cardiac function are the result of both regulation of cardiac-specific genes by $T_3$ [10] and changes in hemodynamic function induced by $T_3$ [11]. The contractile properties of the heart are dependent on the relative amounts of the products of the various myosin genes [8, 12]. Thyroid hormone exerts marked effects on cardiac contractility through changes in the expression of thyroid hormone-responsive genes as well as through alterations in function of important regulatory proteins [1, 2]. It has been demonstrated that a variety of proteins in the cardiac myocyte, including the α- and β-myosin heavy chains, β-adrenergic receptors, sarcoplasmic reticulum (SR) calcium-activated adenosine triphosphatase (SERCA2), and phospholamban (PLB), calcium transporter proteins are regulated by thyroid hormone [12, 13]. The classically described cellular actions of thyroid hormone are mediated by nuclear triiodothyronine (T3) receptors that function to regulate the expression of specific cardiac genes [8, 10] such as plasma membrane sodium potassium ATPase [14] and voltage-activated K1 channel genes including Kv4.2, Kv4.3, and Kv1.5 [15].

In the ventricle, the transcription of the beta myosine heavy chain (β-MHC) antisense (AS) gene appears to be associated with and linked to the transcription of the α-MHC gene; both are induced in the presence of T3. However, in atria this expression appears to be uncoupled. As observed in the ventricles, the expression of the β-MHC AS gene in the atria is inversely correlated, while the expression of the α-MHC gene is not thyroid hormone responsive and highly expressed in all thyroid states. This observation demonstrates for the first time that the previously identified shared promoter region that lies in the intergenic region between the b-MHC and a-MHC genes is differentially regulated in a tissue-specific manner [10]. Exploration of the differences in cofactors and potential epigenetic influences in this shared intergenic promoter region in atria and ventricles may provide additional information regarding the potential mechanism by which T3 influences the MHC genes in the human heart [12].

## Non Genomic Action of Thyroid Hormone on Heart

In addition to the well-characterized nuclear effects of thyroid hormone, some cardiac responses to thyroid hormone appear to be mediated through non genomic mechanisms [16], as suggested by relatively rapid onset of action-faster than can be accounted for by changes in gene expression and protein synthesis and failure to be affected by inhibitors of gene transcription. The significance of these diverse actions remains to be established, but may explain the ability of acute T3 to alter cardiovascular hemodynamics. They may alter the functional proprieties of membrane ion channels and pumps, including the sodium channel and inward rectifying potassium current (IK) [17].

## Electrophysiology and Mechanism of Action of T3 on the Atria

Thyroid hormones have profound effects on the cardiovascular system. The mechanism of pacemaker activity in adult cardiac tissue is increasingly well documented. Although there is some controversy regarding the relative contributions of various ionic currents, it is becoming clear that a variety of ionic currents are responsible for pacemaker activity in various regions of the heart. Sun et al. [18] demonstrated through electrophysiological recordings that thyroid hormone increases the pacemaker rate of these myocytes by increasing the slope of spontaneous depolarization. Under voltage clamp conditions, Sun et al. focused on several ionic currents that may be involved in pacemaker activity in atrial cells, including *I*Ca, *I*f and *I*Na/Ca. of the ionic currents studied, the electrogenic Na+–Ca2+ exchange current was the only candidate to be changed by T3 and which may have altered the slope of spontaneous depolarization. They suggest that, of the ionic currents studied, T3 might accelerate diastolic depolarization and pacemaker activity (at least in part) by an up-regulation of the Na+–Ca2+ exchanger.

Several ionic currents may contribute to pacemaker activity in this tissue, including *I*f, the delayed rectifier potassium current (*I*K) [19–21], both the L-type (*I*Ca,L) and T-type (*I*Ca,T) calcium currents [20] and a background Na+ current (*I*b) [19]. The electrogenic Na+–Ca2+ exchanger, triggered as a result of SR Ca2+ release, may also contribute to the initial phases of diastolic depolarization in the sinoatrial (SA) node [22]. Thus, the positive chronotropic action of thyroid hormones is potentially caused by modulation of any of these electrogenic ion conductances and/or by alterations in intracellular calcium homeostasis.

Early experimental studies of thyroid hormone effects on transmembrane potentials of sinoatrial node cells and atrial muscle cells showed an increased rate of diastolic depolarization and decreased duration of action potential in thyrotoxic animals, suggesting that conductance of K1 ions may be altered [23, 24].

## Electrophysiology and Mechanism of Action of T3 on the Ventricles

Recent evidence has shown that thyroid hormones exert effects on the cardiovascular system that are not mediated by alterations in gene expression. Sakaguchi and co-workers [25]

showed that T3 caused a shortening of the action potential duration in guinea pig ventricular myocytes by increasing whole cell inward rectifier potassium current (*I*K1).

In the rat ventricular myocyte, two primary depolarization-activated outward currents are important in regulating action potential duration: the Ca21-independent transient outward K1 current (*I*to) and a slowly inactivating K1 current (*I*K) [26].

Although thyroid hormone has been shown to regulate the expression of numerous cardiac-specific genes, Sun et al. [27] show that T3 shortens the action potential duration (APD) in hypothyroid rats due at least in part to the increase of the delayed rectifier current *I*K. The *I*to appears to be regulated by thyroid hormone at the transcriptional level, whereas the *I*K is regulated by a nongenomic mechanism of action.

## Relation Between Thyroid Hormone and Adrenergic System

Many of the cardiovascular manifestations of thyroid hormone excess resemble those produced by sympathoadrenal stimulation. Since plasma catecholamine levels and turnover rates are not increased in hyperthyroidism [28], it has been argued that the effects of thyroid hormone result partly from increased responsiveness to catecholamines. This hypothesis is supported by studies that indicate that β-aderenergic receptor (βAR) number and sensitivity are increased in isolated hearts and cultured cells from experimental animals (most often the rat) treated with thyroid hormone [29, 30]. The influence of thyroid hormone on adrenergic responsiveness is particularly controversial in large animals and humans but Brian et al. [31] suggest that the cardiac mechanical effects of hyperthyroidism cannot be explained by enhanced sensitivity to catecholamines. Despite significant increases in basal heart rate and rates of left ventricular (LV) contraction and relaxation, the response to β-adrenergic agonists was not increased in hyperthyroid baboons. Increased basal indices of LV contraction and relaxation in this model are more clearly related to changes in myosin heavy chain isoform expression and the relative abundance of the sarcoplasmic reticulum (SR) calcium pumps (SR $Ca^{2+}$-ATPase) and its phosphoprotein inhibitor, phospholamban, although other thyroid hormone–mediated effects, such as those reported for L-type calcium channels and $Na^{+}/K^{+}$-ATPase pumps cannot be excluded.

Thyroid hormone potentiates the effect of adrenergic system on heart. Catecholamine levels are either normal or decreased in thyrotoxicosis. Facilitation of action of catecholamines is by increasing tissue sensitivity by increased transcription of beta adrenergic receptors and structural similarity to catecholamines. Hyperthyroidism is associated with reduced vagal activity and reduced heart rate variability which can persist despite restoration of euthyroidism [32]. Ojamaa et al. [33] indicate that an analysis confined to the changes in 13-adrenergic receptor expression is insufficient to ascertain the role of catecholamines as mediators of thyroid hormone--dependent effects on cardiac autonomic responsiveness. It is important to consider all three components, the β3-adrenergic receptor, G-coupled protein, and catalytic subunit expression, in assessing adrenergic responsiveness of target tissues.

## Mechanism Underlying the Effect of Thyroid Hormone (TH) on the Arrhythmogenesis

Thyroid hormone has been shown to have several cardiovascular effects, and hyperthyroidism has been known to be an important factor in the etiology of atria and ventricles arrhythmias [5]. In fact, there are always three main ingredients required for the production of a clinical arrhythmia: (1). the arrhythmogenic substrate; (2). the trigger factor; (3). the modulation factors of which the most common is the autonomic nervous system [34]. The cardiovascular manifestations of thyroid dysfunction is due to three potential mechanisms by which thyroid hormones might exert their cardiovascular actions by direct effects at the cellular level, by interacting with the sympathetic nervous system, through alterations of the peripheral circulation and

energy metabolism [5]. Thyroid hormones have been shown to alter cardiac excitability, which may lead to arrhythmias [8].

## Effects of Thyroid Hormones Excess on the Atrias

Hyperthyroidism has been known to be an important factor in the etiology of paroxysmal atrial fibrillation (AF) [5]. The pathogenesis of AF in these patients is postulated to result from shortening of the action potential (AP) duration in the atrial myocardium from excess thyroid hormone facilitating formation of multiple reentry circuits [35, 36]. Graves' disease is one of the most common causes of hyperthyroidism. The prevalence of AF in patients with Graves' disease, as in all other forms of hyperthyroidism, increases with age [36]. Shortening of the AP duration also decreases the refractoriness of cardiomyocytes, which may facilitate the maintenance of multiple reentrant circuits in heart. Using voltage clamp methods, several ionic currents have been investigated in cardiomyocytes. Calcium currents and delayed rectified potassium currents of ventricular cardiomyocytes were increased in hyperthyroidism [37]. Moreover, transient outward potassium currents and inward rectified currents have also been demonstrated to be increased in hyperthyroid ventricular cardiomyocytes [36].

Pulmonary veins (PVs) have been demonstrated to be important sources of ectopic beats with the initiation of paroxysmal AF or the foci of ectopic atrial tachycardia and focal AF [38]. Previous studies have demonstrated that PVs have pacemaker cells in several species [39]. Thyroid hormone changes the electrophysiological activity of the Pulmonary vein cardiomyocytes. Increased automaticity and enhanced triggered activity may increase the arrhythmogenic activity of PVs in hyperthyroidism [36]. Chen et al. suggest in their study that the electrophysiological features of paroxysmal AF associated with hyperthyroidism are essentially different from those of lone paroxysmal AF. In patients with paroxysmal AF and hyperthyroidism, a shortening of the refractory period in association with a facilitation of the atrial conduction delay could be expected to increase the propensity for AF, and a pre-existent arrhythmogenic substrate might not be essential to the genesis of AF. These findings suggest that the agents that prolong the atrial effective refractory period are effective against AF in patients with hyperthyroidism [40].

## Effects of Thyroid Hormones Excess on the Ventricles

The onset of tachycardia or ventricular fibrillation (VF) has been reported within a thyrotoxic storm [41]. The presentation of these arrhythmias in the initial phase of the disease is much less common, and only a few isolated cases are described in the scientific literature. The majority [42, 43] occur in the context of thyrotoxic periodic paralysis with severe hypokalemia [44]. There has been an occasional patient in whom the ventricular arrhythmia were related to coronary spasm [45].

Nevertheless, the shortening of the Q–T interval and the effect of TH on the autonomic nervous system may affect ventricular arrhythmogenesis [46]. TH interacts with the sympathetic nervous system by altering responsiveness to sympathetic stimulation presumably by modulating adrenergic receptor function and/or density [5]. The density of myocardial adrenergic binding sites has been shown to be enhanced by chronic as well as acute treatment with thyroid hormone in hypothyroidism [47]. Thyroid hormone, in addition, induces a rate-dependent lengthening of the Purkinje fiber action potential while ventricular action potential shortens [48]. Consequently, these differences can enhance dispersion of myocardial repolarization and facilitate re-entrant arrhythmias including ventricular fibrillation (VF) [49]. It should also be noted that hyperthyroidism may affect myocardial electrical stability [50] due to increased excitability linked to triggered activity [51] resulting in ventricular premature beats (VPB) [52] that often initiate malignant arrhythmias [53].

On the other hand, it has been suggested that hypothyroidism might confer a protection against arrhythmias because they are rarely encountered in hypothyroid patients. Only atrioventricular blocks, sinus bradycardia, and rare episodes of "torsade de pointes" have been reported to be associated with clinical hypothyroidism [3]. In an animal model of ventricular fibrillation, hypothyroidism has been shown to increase the fibrillatory threshold of the ventricles [5].

In humans, the prolongation of the QTc interval encountered in hypothyroid patients is similar to that seen in euthyroid patients on class III antiarrhythmic agents [54]. In this regard, it has been suggested that the antiarrhythmic effect of amiodarone parallels its blocking effect on the peripheral thyroid hormone metabolism, suggesting that tissue hypothyroidism may have some antiarrhythmic properties [55]. However, this concept has been challenged by several observations. Tri-iodothyronine T3 administration to euthyroid patients treated with amiodarone for benign atrial or ventricular arrhythmias does not increase the frequency of arrhythmias [52]. In patients with hypothyroidism, thyroid replacement therapy did not increase significantly the frequency of benign atrial or ventricular premature beats [56].

Many patients with overt hypothyroidism have Q–T interval lengthening, which reflects the prolonged ventricular action potential due to electrical remodeling [57]. It renders the heart prone to ventricular arrhythmias, such as potentially lethal polymorphic tachycardia "Torsade de Pointes" [58]. The incidence of arrhythmia precedes the occurrence of early after depolarization (EAD) usually triggered in the setting of hypokalemia. EAD-induced triggered responses are traditionally thought to be involved in the generation of ventricular arrhythmias under long Q–T conditions. Dispersion of ventricular refractoriness resulting from heterogeneous myocardial structural remodeling [59] predisposes to Q–T dispersion and consequently to ventricular arrhythmias particularly in patients with subclinical hypothyroidism that are treated with L-thyroxine [60]. Furthermore, in hypothyroidism an atrioventricular block of different degrees may occur [61]. Nevertheless, the VF incidence is reduced in hypothyroidism [62] depression of TH levels seems to be beneficial in patients with angina and acute myocardial infarction [53, 63].

Finally, thyroid hormones may trigger arrhythmias mostly at the level of the atria, and there is some evidence that tissue hypothyroidism may increase the fibrillation threshold of the ventricles. However, there are no clear data in humans indicating that hypothyroidism confers a protection against ventricular or atrial arrhythmias [5].

## Supraventricular Arrhythmia

### Atrial Arrhythmia

The atrial arrhythmia includes AF, atrial flutter and atrial tachycardia. Atrial fibrillation is the most frequent atrial arrhythmia. Hyperthyroidism has been associated with atrial tachyarrhythmias [64] and with sustained AF occurring in 20–30 % of patients even after return to the euthyroid state [64]. The risk of atrial fibrillation or flutter in hyperthyroidism was higher in men than in women, and the risk of atrial fibrillation in hyperthyroidism increased by increasing age during the age range of 20–89 years. The presence of ischemic heart disease, congestive heart failure, and heart valve disease was also associated with an increased risk of atrial fibrillation [65].

We could not differentiate atrial fibrillation from atrial flutter because in the literature and a lot of articles didn't differentiate the two arrhythmias. In fact, they had the same ICD-10 code [66]. In other hand, there is a low proportion of patients with pure atrial flutter these represent approximately 5 % of the recorded cases [37–39, 67].

#### Hyperthyroidism

Thyrotoxicosis is a common disorder with a prevalence of 3 % in females and 0.3 % in males in iodine-replete areas such as the United Kingdom and the United States [68]. It is known to induce many cardiovascular effects such as sinus tachycardia, systolic hypertension, changes in ventricular systolic and diastolic function, and

predisposition to dysrhythmias, especially AF [6]. The prevalence of AF in patients with hyperthyroidism ranges between 2 and 20 %, and the risk is approximately sixfold greater than normal population [69].

The first step in the management of atrial fibrillation, despite the cause, is to control the ventricular response. β-blockers are one of the mainstays of treatment of AF in the setting of hyperthyroidism [69]. Selective or non-selective β-blockers can provide rapid symptom relief by reducing the ventricular rate, but these agents are unlikely to convert AF to sinus rhythm as they have little effect on hyperthyroidism, the primary cause of cardiac stimulation and AF. Therefore, restoration of euthyroidism by radioiodine or anti-thyroid drugs is the ultimate treatment of choice for long-term AF management in this setting. Successful treatment of hyperthyroidism with either radioiodine or thioureas is associated with a reversion to sinus rhythm in a majority of patients within 2–3 months [70]. Zhen-Hu Zhou et al. demonstrated in their study that after euthyroidism or hypothyroidism states were achieved, very frequent paroxysmal AF were observed and no recurrence was noted at the end of the follow-up. Persistent AF, however, spontaneously converted to sinus rhythm in only 40 % of the patients, but persistent AF continued in the remaining patients. Further analysis showed that older age (>55 years) and a long duration of hyperthyroidism of more than 5 years, and a long duration of pre-treatment AF are independent predictors for continued AF following the successful treatment of hyperthyroidism [71]. In other hand, Xiao et al. suggested that Blockade of angiotensin II could improve abnormal atrial electrophysiological properties and further reduce AF vulnerability by extenuating ion channel, gap junction and structural remodeling in experimental thyrotoxic rabbits [72].

The management strategies for persistent AF following hyperthyroidism treatment are not entirely clear. The current recommendations are that after the patient has been rendered chemically euthyroid, electrical or pharmacological cardioversion should be attempted [69].

Elective cardioversion for persistent AF is highly effective and sinus rhythm maintenance rates are greater than 50 % over 10 years. The addition of anti-arrhythmic drugs may also help to maintain sinus rhythm in these patients [73]. Bepridil is as beneficial treatment to convert AF for the patients with hyperthyroidism-induced persistent AF as it is for the patients with AF due to other causes [74]. Yo Kunii et al. showed that bepridil converted hyperthyroidism-induced persistent AF to sinus rhythm as much as it does after a long duration of AF due to other causes, and the sinus rhythm maintenance rate was very high. Bepridil is very beneficial medicine for the patient of hyperthyroidism-induced AF, however, it should be used with caution, and frequent or continuous ECG monitoring is necessary, to avoid serious side effects [74].

## Subclinical Hyperthyroidism and Atrial Fibrillation

Sub clinical hyperthyroidism is defined as low serum thyrotropin concentration in an asymptomatic patient with normal serum T3 and T4 concentration. It has a prevalence of 0.5–3.9 % in adults [75]. The prevalence of atrial fibrillation in patients with low serum thyrotropin concentration was 13.3 % compared to 2.3 % in persons with normal values. The relative risk of atrial fibrillation in subjects with low serum thyrotropin and normal free T3, T4 values compared to those with normal serum thyrotropin was 5.2 [32]. Osturk et al. [76] showed that left atrial mechanical and electromechanical function in subclinical thyroid disorders was impaired. TSH was an independent determinant of interatrial delay. Prolonged atrial electromechanical coupling time and impaired mechanical atrial functions may be related to the increased incidence of arrhythmias.

## Hypothyroidism and Subclinical Hypothyroidism

Hypothyroidism is associated with cardiovascular risk factors, subclinical cardiovascular disease, and overt cardiovascular disease, all of which predispose to AF. Subclinical hypothyroidism was common. In fact, the prevalence was

4–8 % in people older than 60 years of age. Subclinical hypothyroidism has some clinical consequences like an increase in the prevalence of atria fibrillation [77]. However, Klemperer et al. [78] found that perioperative T3 administration in Cardiopulmonary bypass in euthyroid patients decreased the incidence and need for treatment of postoperative atrial fibrillation. This finding still unexplained. Kim et al. [79] did not identify a significant association between hypothyroidism and 10-year risk of incident AF in a community-based study from the Framingham heart study.

### Euthyroid Range in Older Adults

Cappola et al. [80] examined the relationship between thyroid function testing within the euthyroid range and outcomes encompassing the cardiovascular system in cohort of community-dwelling individuals aged 65 years and older. They found increased risk of atrial Fibrillation at higher concentrations of FT4 and they suggested that there is no optimal set of thyroid function tests within current reference ranges to reflect the euthyroid ideal in the age group. Cappola et al. [80] proposed that the optimal TSH may need to be higher in older people than the currently defined references ranges.

### Should We Anticoagulate and Attempt Cardioversion in Those with AF?

Anticoagulation of patients with hyperthyroidism and AF is controversial [81] as the risk for systemic thromboembolic events in the setting of thyrotoxicosis is not well defined [82], and anticoagulation drugs such as warfarin, are associated with a significant risk of bleeding complications and other side effects [82]. There are beliefs that in patients with hyperthyroidism it is advancing age rather than the presence of AF that is the main risk factor [81] for a thromboembolic event, and in younger patients without organic heart disease, hypertension, or other independent risk factors for embolization, the benefits of anticoagulation may actually be outweighed by the risks [69]. In our knowledge, no interaction between thyroid function and unfractionated heparin (UFH) has been documented, however Badawi [83] reported an interaction between thyroid function and UFH. Nakazawa et al. [84] suggested that spontaneous reversion of atrial fibrillation to sinus rhythm is highly unlikely if the duration of atrial fibrillation before the euthyroid state is achieved exceeds 13 months, or if it is still present after the patient has been in a euthyroid state for 4 months, Cardioversion should be performed at about the 16th week after the euthyroid state is achieved.

### Arrhythmia and Amiodarone-Induced Hyperthyroidism

Amiodarone is the most commonly used antiarrhythmic drug worldwide [85]. It is effective in the treatment of both supraventricular and ventricular tachyarrhythmias and has the added advantage of being well tolerated in patients with both normal and impaired left ventricular systolic function [85]. The majority of patients (>70 %) on amiodarone will remain euthyroid. However, treatment may lead to either amiodarone-induced hypothyroidism (AIH) or amiodarone-induced thyrotoxicosis (AIT), with AIH more common in iodine-sufficient populations and AIT in iodine-deficient populations [86].

Amiodarone-induced thyroid dysfunction occurs in 15–20 % of amiodarone-treated patients [87]. Amiodarone-induced hypothyroidism (AIH) does not pose relevant problems, is easily controlled by L-thyroxine replacement, and does not require amiodarone withdrawal. Most frequently, AIH develops in patients with chronic autoimmune thyroiditis. Amiodarone-induced thyrotoxicosis (AIT) is most frequently due to destructive thyroiditis (type 2 AIT) causing release of thyroid hormones from the damaged, but otherwise substantially normal gland. Less frequently AIT is a form of hyperthyroidism (type 1 AIT) caused by the iodine load in a diseased gland (nodular goiter, Graves' disease). A clear-cut differentiation between the two main forms is not always possible, despite recent diagnostic advances. As a matter of fact, mixed or indefinite forms do exist, contributed to by both thyroid damage and increased thyroid hormone

synthesis. Treatment of type 1 (and mixed forms) AIT is based on the use of thionamides, a short course of potassium perchlorate and, if treatment is not rapidly effective, oral glucocorticoids. Glucocorticoids are the first-line treatment for type 2 AIT. Amiodarone should be discontinued, if feasible from a cardiac standpoint. Continuation of amiodarone has recently been associated with a delayed restoration of euthyroidism and a higher chance of recurrence after glucocorticoid withdrawal. Whether amiodarone treatment can be safely reinstituted after restoration of euthyroidism is still unknown. In rare cases of AIT resistance to standard treatments, or when a rapid restoration of euthyroidism is advisable, total thyroidectomy represents a valid alternative. Radioiodine treatment is usually not feasible due to the low thyroidal iodine uptake [4]. Dronedarone was approved in 2009 for the treatment of patients with atrial fibrillation. Like amiodarone, dronedarone is a benzofuran derivative with similar electrophysiologic properties. In contrast to amiodarone, however, dronedarone is structurally devoid of iodine and has a notably shorter half-life. Dronedarone proved to be associated with significantly fewer adverse effects than amiodarone, making it a more attractive choice for patients with atrial fibrillation or flutter, who are at risk of developing amiodarone-induced thyroid dysfunction [88].

## Other Supraventricular Arrhythmia

Biondi et al. [46] reported the possibility that thyroid hormones may also induce other kinds of supraventricular arrhythmias not frequently described in hyperthyroid patients, such as reentrant atrioventricular (A-V) nodal tachycardia. This report also showed that reentrant A-V nodal tachycardia may be triggered by thyroid hormone in predisposed subjects. The reentrant A-V nodal tachycardia is a relatively common cause of regular, narrow QRS complex tachycardia, and it is more prevalent in women than in men with a ratio of 7:1 respectively [89]. Epidemiologically, it must be emphasized that both thyroid disease and reentrant A-V nodal tachycardia are highly prevalent in females.

In patients with reentrant A-V nodal tachycardia, at least two functionally distinct A-V nodal conduction patterns are demonstrable [90, 91]. One pathway, referred to as the fast pathway, is characterized by rapid conduction velocity and relatively long refractoriness. The second or slow pathway typically shows slow conduction velocity and short refractoriness. During sinus rhythm, the electric impulse is expected to reach the His bundle and the ventricle preferentially over the faster-conducting pathway with the frequent evidence of a short P-R interval. A-V nodal reentry of the common type (slow-fast) is typically initiated by an atrial premature beat that conducts down only through the slow pathway because of functional block of the fast pathway, and reenters back through the fast pathway because of recovery of its excitability. Conceivably, thyroid hormones might increase the occurrence of reentrant A-V nodal tachycardia in predisposed subjects because of the enhancement of atrial excitability, with consequent increase of the number of atrial premature beats and the shortening of the refractory period of the conducting tissues. Thus, reentrant A-V nodal tachycardia might be triggered in patients in whom L-T4 is exogenously administered to lower TSH [46].

Abbasoglu et al. [92] reported a case of Neonatal thyrotoxicosis with concurrent supraventricular tachycardia caused by the transplacental passage of thyroid stimulating immunoglobulins from mothers with Graves' disease. The heart rate was between 260 and 300 beats/min. Matthew et al. [93] described a case of 43 year old woman who presented in supraventricular tachycardia and acute pulmonary edema and died without any evident cause of mortality. At autopsy the significant positive macroscopic findings were confined to the lungs (acute pulmonary edema) and thyroid (diffusely enlarged). Histology revealed features typical of Graves' disease while post mortem thyroid function tests supported a diagnosis of thyrotoxic crisis in the setting of undiagnosed Graves' disease.

## Ventricular Arrhythmia

In contrast to high incidence of atrial arrhythmias in the hyperthyroid status, the ventricular arrhythmias are uncommon and found with a frequency similar to that in the normal population [3, 6, 89, 90]. It is likely because VF is exceptional in those with elevated TH without cardiomyopathy [41, 94, 95]. Thus, the occurrence of ventricular arrhythmias in thyrotoxic subjects during and after antithyroid therapy is rare [3, 6]. However, VF may occur in those with associated heart disease or heart failure of various etiology [5, 26].

## Hyperthyroidism

Ventricular tachycardia (VT) is one of the major causes of death in patients with structural heart disease. Electrical storm (ES) is defined as hemodynamically significant VT occurring at least three times over a 24-h period and requiring delivery of direct current shocks [96]. Determining the etiology of extrastimulus ES is quite challenging and requires detailed evaluation of the patient. The etiology of ES varies and includes enhanced sympathetic tone, myocardial ischemia, electrolyte imbalance, endocrine disorders (pheochromocytoma, thyrotoxycosis, etc.), genetic abnormalities (Brugada syndrome, long-QT syndrome, arrhythmogenic right ventricular dysplasia, etc.). Tachycardia during ES might be monomorphic or polymorphic. Polymorphic ES without QT prolongation is frequently associated with myocardial ischemia [97].

## Subclinical Hyperthyroidism

Subclinical hyperthyroidism exerts many significant effects on the cardiovascular system; it is usually associated with a higher heart rate and a higher risk of supraventricular arrhythmias, and with an increased left ventricular mass, often accompanied by an impaired diastolic function and sometimes by a reduced systolic performance on effort and decreased exercise tolerance. It is well known that these abnormalities usually precede the onset of a more severe cardiovascular disease, thus potentially contributing to the increased cardiovascular morbidity and mortality observed in these patients [98]. To our knowledge, the literature has not reported ventricular arrhythmias caused by subclinical hyperthyroidism.

## Hypothyroidism

It is well known that an excess or deficit of thyroid hormones affects the cardiovascular system. A typical ECG in hypothyroidism shows bradycardia, a low voltage of the QRS complexes, elongation of the QT and flattening or inverting of the T waves. However, less well known is the fact that hypothyroidism may be the cause of atrioventricular blocks and of acquired long QT syndrome (LQTS). Only few publications reported life-threatening by possibility of torsade de pointes (TdP) type tachycardia and ventricular fibrillation occurring in patients with prolonged QT syndrome in the course of hypothyroidism [99].

Profound hypothyroidism and decreased expression of tri-iodothyronine in the heart cells may cause a worsening of cardiac contractility, a decreasing heart rate and a slowing down of the conduction of electrical stimuli in the heart muscle. This may be the reason for bradycardia and elongation of the QT interval and, in consequence, life-threatening arrhythmias may occur, for example TdP-type tachycardia. Decreased triiodothyronine expression and electrolyte disorders such as moderate hypokalaemia and hypocalcaemia probably prompted LQTS and shock in this case [99]. It is important to note that amiodarone was not sufficiently effective to prevent recurrent ventricular arrhythmias. Few publications reported that lidocaine or bretylium tosylate may interrupt this kind of paroxysmal tachycardia and endocavitary electrode stimulation [62].

Hypothyroidism may be the cause of life-threatening arrhythmias secondary to acquired

long QT syndrome. Ventricular electrostimulation was a life-saving procedure in this case of prolonged QT syndrome. The use of temporary ventricular electrostimulation protected the patient against dangerous ventricular arrhythmias, while balancing the deficiency of thyroid hormones and electrolytes [31].

## Subclinical Hypothyroidism

Subclinical hypothyroidism is a common disorder characterized by elevated serum thyroid-stimulating hormone, normal free thyroxine and free triiodothyronine levels. Its prevalence reportedly ranges between 1.3 and 17.5 %, depending on age, gender and the amount of iodine exposure [100]. Bakiner et al. detected prolonged QT intervals and increased QTc among their subclinical hypothyroid cases. The prolongation remained significant for the whole group, as well as within the subgroups. There was a positive correlation between TSH levels and QTc. Return of serum TSH levels from 110 mIU/l to values within the reference range resulted in normalization of QTc. Such an outcome for patients with TSH between 5 and 10 mIU/l remains to be investigated [101]. TSH concentration has a role in ventricular inhomogeneity and, therefore, subclinical hypothyroidism may predispose to ventricular arrhythmias [60].

**Conclusion**

Thyroid hormones may trigger arrhythmias mostly at the level of the atria. The incidence of cardiac arrhythmias is in relation to the altered thyroid status. It appears that hypothyroidism is mostly associated with reduced probability of cardiac arrhythmias unlike hyperthyroidism that increases a risk notably for atrial and to a lesser extent ventricular arrhythmias that occur particularly in a cardiomyopathic heart. The long-term arrhythmia depends of the precocity of thyroid disease treatment and cardiomyopathic heart.

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