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ARRHYTHMOGENIC EFFECTS OF THYROID HORMONE EXCESS: FROM MOLECULAR MECHANISMS TO CLINICAL OUTCOMES

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Abstract : Thyroid hormone excess exerts profound effects on the cardiovascular system, significantly increasing the risk of cardiac arrhythmias. Hyperthyroidism is commonly associated with supraventricular arrhythmias, particularly atrial fibrillation, but may also predispose to ventricular rhythm disturbances. This review aims to provide a comprehensive overview of the arrhythmogenic effects of thyroid hormone excess, focusing on molecular, electrophysiological, and clinical aspects. Thyroid hormones, particularly triiodothyronine (T3), influence cardiac electrophysiology through multiple pathways, including upregulation of β-adrenergic receptors, modulation of ion channel expression, increased Na^+/K^+-ATPase activity, and altered intracellular calcium handling. These changes result in shortened action potential duration, increased automaticity, enhanced triggered activity, and facilitation of reentry mechanisms. Clinically, atrial fibrillation remains the most prevalent arrhythmia, associated with a higher risk of thromboembolic complications. Early recognition and appropriate management of thyroid dysfunction significantly reduce arrhythmia burden and improve patient outcomes. Hyperthyroidism should therefore be considered a reversible yet potentially serious cause of cardiac arrhythmias, highlighting the importance of integrating molecular insights into clinical practice for optimal diagnostic and therapeutic strategies.

Keywords : hyperthyroidism, thyroid hormone excess, cardiac arrhythmias, atrial fibrillation, arrhythmogenesis, cardiac electrophysiology, β-adrenergic receptors, ion channel modulation, calcium handling, action potential duration, automaticity, reentry mechanisms, thyrotoxicosis, cardiovascular complications, reversible causes of arrhythmia

Introduction: Thyroid hormones play a critical role in the regulation of cardiovascular physiology, influencing heart rate, myocardial contractility, vascular tone, and cardiac electrophysiology. Excess production of thyroid hormones, as observed in hyperthyroidism, leads to a hypermetabolic state that profoundly affects the cardiovascular system. Among these effects, the development of cardiac arrhythmias represents one of the most clinically significant and potentially life-threatening complications. Hyperthyroidism is strongly associated with an increased incidence of supraventricular arrhythmias, particularly atrial fibrillation, which may occur in up to 10–20% of patients depending on age and comorbidities. In addition to atrial fibrillation, patients may present with sinus tachycardia, atrial flutter, premature atrial contractions, and, less commonly, ventricular arrhythmias. These rhythm disturbances not only impair hemodynamic stability but also significantly increase the risk of thromboembolic events, heart failure, and mortality.

The arrhythmogenic effects of thyroid hormone excess are mediated through complex molecular and electrophysiological mechanisms. Triiodothyronine (T3), the biologically active form of thyroid hormone, modulates gene expression and directly influences ion channel activity in cardiomyocytes. It enhances β-adrenergic receptor sensitivity, increases sympathetic tone, and alters intracellular calcium dynamics. Furthermore, thyroid hormones shorten the duration of the cardiac action potential and refractory period, thereby facilitating abnormal impulse formation and reentrant circuits. Despite the well-established association between hyperthyroidism and arrhythmias, the underlying mechanisms remain incompletely understood, and their clinical implications continue to evolve. Importantly, hyperthyroidism represents a potentially reversible cause of arrhythmias, emphasizing the need for timely diagnosis and targeted therapy. Early recognition and appropriate management of thyroid dysfunction can lead to significant improvement or complete resolution of rhythm disturbances.

This review aims to explore the arrhythmogenic effects of thyroid hormone excess from a comprehensive perspective, integrating molecular mechanisms with electrophysiological alterations and clinical manifestations. By bridging basic science and clinical practice, this article seeks to provide a deeper understanding of the pathogenesis, diagnosis, and management of arrhythmias associated with hyperthyroidism.

Molecular and Electrophysiological Mechanisms

The arrhythmogenic potential of thyroid hormone excess arises from a complex interaction of genomic and non-genomic effects on cardiac tissue. Triiodothyronine (T3), the active form of thyroid hormone, regulates the transcription of multiple cardiac genes, leading to structural and functional remodeling of cardiomyocytes. These genomic effects are complemented by rapid, non-genomic actions that directly influence ion transport and cellular electrophysiology. At the molecular level, T3 increases the expression and sensitivity of β-adrenergic receptors in the myocardium, thereby amplifying the effects of circulating catecholamines. This heightened adrenergic responsiveness enhances cyclic adenosine monophosphate (cAMP) signaling, which in turn modulates multiple ion channels and calcium-handling proteins. As a result, there is an increase in heart rate, myocardial excitability, and conduction velocity.

Thyroid hormones also exert significant effects on cardiac ion channels. They upregulate sodium-potassium ATPase activity and influence the expression of voltage-gated potassium channels, leading to accelerated repolarization. This results in shortening of the action potential duration and a reduction in the effective refractory period. Such changes create a substrate that is highly susceptible to reentrant arrhythmias. In addition, alterations in L-type calcium channel activity and enhanced sarcoplasmic reticulum calcium cycling contribute to increased intracellular calcium levels, promoting delayed afterdepolarizations and triggered activity.

Another important mechanism involves the modulation of pacemaker activity. T3 increases the automaticity of sinoatrial nodal cells by enhancing the funny current (If) and calcium-dependent depolarizing currents. This leads to sinus tachycardia and facilitates the initiation of ectopic atrial activity. Furthermore, increased dispersion of repolarization across myocardial tissue creates electrophysiological heterogeneity, which further predisposes to arrhythmia formation. In atrial tissue, these changes are particularly pronounced, explaining the strong association between hyperthyroidism and atrial fibrillation. Structural remodeling, including mild atrial dilation and fibrosis in chronic cases, may further stabilize reentrant circuits. Although ventricular arrhythmias are less common, they may occur in the presence of underlying heart disease or severe thyrotoxicosis.

Overall, thyroid hormone excess promotes arrhythmogenesis through a combination of enhanced automaticity, triggered activity, and reentry mechanisms. These electrophysiological

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alterations, together with increased sympathetic drive, create a highly arrhythmogenic environment. Understanding these mechanisms is essential for developing targeted therapeutic strategies and improving clinical outcomes in patients with hyperthyroidism.

Clinical Manifestations

The clinical expression of arrhythmias in hyperthyroidism varies widely depending on patient age, duration of thyrotoxicosis, and the presence of underlying cardiovascular disease. Among all rhythm disturbances, atrial fibrillation represents the most frequent and clinically significant manifestation. It is particularly prevalent in older patients and in those with subclinical hyperthyroidism, where even mild elevations in thyroid hormones may predispose to arrhythmia development. In younger individuals, sinus tachycardia is often the predominant finding and may be the earliest sign of thyroid hormone excess. Patients with hyperthyroidism-related arrhythmias typically present with palpitations, dyspnea, fatigue, reduced exercise tolerance, and, in some cases, syncope. Atrial fibrillation in this context is often associated with a rapid ventricular response, which can exacerbate myocardial oxygen demand and precipitate ischemia in susceptible individuals. Furthermore, persistent tachyarrhythmias may lead to tachycardia-induced cardiomyopathy, characterized by left ventricular systolic dysfunction and heart failure symptoms. Thromboembolic complications represent a major clinical concern, particularly in patients with atrial fibrillation. Hyperthyroidism has been shown to independently increase the risk of thrombus formation, possibly due to a hypercoagulable state characterized by increased levels of clotting factors and impaired fibrinolysis. As a result, the risk of stroke is significantly elevated, necessitating careful risk stratification and appropriate anticoagulation therapy.

Although less common, ventricular arrhythmias may occur, particularly in severe thyrotoxicosis or in patients with preexisting structural heart disease. These may range from isolated premature ventricular contractions to more serious forms such as ventricular tachycardia. In rare cases, thyrotoxicosis may precipitate sudden cardiac death, highlighting the importance of early recognition and intervention.

Diagnostic Evaluation

The diagnosis of arrhythmias associated with thyroid hormone excess requires an integrated approach combining clinical assessment, laboratory testing, and electrocardiographic evaluation. Measurement of serum thyroid-stimulating hormone (TSH) remains the most sensitive initial test, typically showing suppressed levels in hyperthyroidism. Elevated free thyroxine (FT4) and/or triiodothyronine (FT3) levels confirm the diagnosis. Electrocardiography (ECG) plays a central role in identifying rhythm disturbances. Common findings include sinus tachycardia, atrial fibrillation, atrial flutter, and supraventricular ectopic beats. In some cases, shortened PR interval and increased P-wave amplitude may be observed, reflecting enhanced atrial conduction. Ambulatory Holter monitoring may be useful in detecting paroxysmal arrhythmias and assessing heart rate variability. Echocardiography is recommended to evaluate cardiac structure and function, particularly in patients with persistent arrhythmias or suspected cardiomyopathy. It may reveal left atrial enlargement, increased cardiac output, and, in advanced cases, left ventricular dysfunction. Additional investigations, including thyroid antibody testing and radionuclide imaging, may help determine the underlying etiology of hyperthyroidism.

Risk stratification for thromboembolism, particularly in patients with atrial fibrillation, should be performed using established clinical scoring systems such as CHA_2DS_2-VASc. This is essential for guiding decisions regarding anticoagulation therapy.

Management Strategies

The management of arrhythmias in hyperthyroidism involves a dual approach targeting both the underlying thyroid dysfunction and the arrhythmia itself. Restoration of euthyroid status is the cornerstone of therapy and often leads to significant improvement or complete resolution of rhythm disturbances. Antithyroid medications, such as methimazole or propylthiouracil, are commonly used to reduce thyroid hormone synthesis. In selected cases, radioactive iodine therapy or surgical thyroidectomy may be indicated. The choice of treatment depends on patient-specific factors, including age, comorbidities, and the underlying cause of hyperthyroidism.

Beta-adrenergic blockers play a crucial role in the symptomatic management of arrhythmias. By reducing heart rate and attenuating sympathetic activity, they effectively control palpitations and improve hemodynamic stability. Non-selective beta-blockers, such as propranolol, may offer additional benefits by partially inhibiting peripheral conversion of T4 to T3. In patients with atrial fibrillation, rate control is often the initial strategy, particularly in the acute phase. Rhythm control may be considered after achieving euthyroidism, as spontaneous conversion to sinus rhythm frequently occurs. Electrical cardioversion may be indicated in hemodynamically unstable patients.

Anticoagulation therapy should be initiated based on thromboembolic risk assessment. Direct oral anticoagulants (DOACs) or vitamin K antagonists may be used, depending on clinical context and patient characteristics. Importantly, even in younger patients, hyperthyroidism-associated atrial fibrillation may warrant anticoagulation due to the prothrombotic state.

Discussion

The relationship between thyroid hormone excess and cardiac arrhythmias represents a complex interplay between endocrine and cardiovascular systems. While the association is well established, several aspects of the underlying mechanisms and optimal management strategies remain areas of ongoing research. For instance, the precise contribution of subclinical hyperthyroidism to arrhythmia risk continues to be debated, particularly in younger populations. Recent studies have emphasized the importance of early detection and treatment of thyroid dysfunction in preventing long-term cardiovascular complications. Advances in molecular cardiology have provided deeper insights into the role of ion channel remodeling and calcium handling abnormalities in arrhythmogenesis. These findings may pave the way for the development of targeted therapies aimed at specific electrophysiological pathways. From a clinical perspective, the reversibility of hyperthyroidism-induced arrhythmias represents a unique therapeutic opportunity. However, delayed diagnosis or inadequate treatment may result in persistent arrhythmias and structural cardiac changes that are less responsive to therapy. Therefore, a multidisciplinary approach involving endocrinologists and cardiologists is essential for optimal patient management.

Conclusion: In summary, excess thyroid hormone exerts a multifaceted and potent influence on cardiac rhythm, establishing a clear mechanistic and clinical link between hyperthyroidism and arrhythmogenesis. Through coordinated genomic and non-genomic actions, particularly mediated by triiodothyronine (T3), thyroid hormone excess alters ion channel expression, enhances β-adrenergic sensitivity, and disrupts intracellular calcium homeostasis. These changes collectively create a pro-arrhythmic substrate characterized by increased automaticity, shortened refractory periods, and a heightened susceptibility to reentrant circuits. From a clinical standpoint, atrial fibrillation emerges as the dominant manifestation, carrying substantial risks of thromboembolism, heart failure, and increased mortality. Importantly, hyperthyroidism represents one of the few reversible etiologies of arrhythmias, underscoring the critical importance of early identification and timely restoration of euthyroid status. Failure to recognize and adequately treat thyroid dysfunction may result in persistent electrophysiological remodeling and long-term cardiovascular complications.

Bridging molecular mechanisms with clinical practice remains essential for optimizing patient outcomes. A comprehensive, multidisciplinary approach integrating endocrinological and cardiological expertise allows for precise diagnosis, effective risk stratification, and individualized treatment strategies. Future directions should focus on refining predictive models of arrhythmia risk in both overt and subclinical hyperthyroidism, as well as exploring targeted therapies aimed at specific electrophysiological pathways influenced by thyroid hormones.

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