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EFFECTS OF THYROID HORMONE IMBALANCE ON THE DEVELOPMENT OF CARDIAC ARRHYTHMIA

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Abstract : Thyroid hormones (THs) profoundly influence cardiac electrophysiology, cellular architecture, and hemodynamic performance. Dysregulation of triiodothyronine (T3) and thyroxine (T4)—whether overt or subclinical—produces multilayer remodeling ranging from ion-channel transcription to autonomic imbalance, creating an arrhythmogenic substrate. Hyperthyroidism accelerates depolarization kinetics, shortens action potential duration (APD), enhances β-adrenergic responsiveness, and increases intracellular Ca^{2+} cycling, predisposing to atrial fibrillation (AF) and supraventricular tachyarrhythmias. Conversely, hypothyroidism prolongs repolarization, disrupts Ca^{2+} reuptake, induces myocardial stiffness, and increases susceptibility to bradyarrhythmias and torsadogenic ventricular arrhythmias. This article integrates genomic, non-genomic, electrophysiological, structural, and hemodynamic pathways linking TH dysregulation to cardiac arrhythmogenesis, bridging molecular physiology with clinical electrophysiology.

Keywords : cardiac arrhythmia, atrial excitability, sinus tachycardia, hyperthyroidism, hypothyroidism

Thyroid hormone plays an important role in cardiac electrophysiology and Ca^{2+} handling through both genomic and nongenomic mechanisms of action, while both actions can interfere. Chronic changes in the amount of circulating thyroid hormone due to thyroid dysfunction or systemic disease result in structural, electrophysiological and Ca^{2+} handling remodeling, while acute changes may affect basal activity of cardiac cells membrane systems. Consequently, long-term or rapid modulation of sarcolemmal ion channels, Ca^{2+} cycling proteins and intercellular communicating channels by thyroid hormone may affect heart function as well as susceptibility of the heart to arrhythmias.

Cardiac myocytes express specific TH receptors—TRα1 predominantly in the myocardium and TRβ1 more broadly—linking systemic endocrine fluctuations directly to cardiomyocyte signaling. Even minimal shifts in serum free T3/T4, including within the subclinical range, dynamically alter conduction velocity, refractory periods, and atrial structural integrity. Thus, TH dysregulation is not merely a comorbidity—it is an independent electrophysiological determinant of cardiac arrhythmias. The following sections delineate the multilayer mechanisms responsible for these disturbances.

Molecular and Genomic Dysregulation of Thyroid Hormone Signaling

1.Genomic Effects

AMERICAN ACADEMIC PUBLISHER
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Thyroid hormones (mainly T3) diffuse across the cardiomyocyte membrane and bind to nuclear thyroid hormone receptors TRα1 and TRβ1, which function as transcription factors. In the heart, TRα1 is the dominant isoform, creating a highly sensitive genomic environment for T3 fluctuations. Upon binding T3, these receptors interact with thyroid response elements (TREs) on DNA and regulate expression of numerous ion-handling, contractility, and metabolic genes.

Upregulated in the Hyperthyroid State

a. Na^+/K^+-ATPase

- Increased synthesis enhances repolarization efficiency.
- Higher pump activity reduces intracellular Na^+, indirectly affecting the Na^+/Ca^{2+} exchanger (NCX) and promoting increased Ca^{2+} cycling, contributing to increased automaticity and contractility.

b. β_1-Adrenergic Receptors

- T3 increases receptor density and post-receptor signaling (Gs protein, adenylyl cyclase).
- Myocardium becomes hypersensitive to circulating catecholamines → tachyarrhythmia, atrial ectopy, AF initiation.

c. Voltage-Gated K^+ Channels. T3 strongly increases transcription of several repolarizing potassium currents

HCN2/HCN4 Channels

- T3 upregulates If-channel transcription.
- Enhances slope of spontaneous diastolic depolarization in SA node. Causes sinus tachycardia, premature atrial contractions, AV nodal reentrant tendencies.

d. SERCA2a (with reduced phospholamban inhibition)

- Increased Ca^{2+} reuptake into the sarcoplasmic reticulum (SR)
- Allows faster relaxation (lusitropy) and faster cycling of Ca^{2+} needed for tachycardia
- Indirectly increases risk of Ca^{2+}-driven triggered activity (delayed afterdepolarizations).

2. Non-Genomic Pathways

Thyroid hormones (THs), in addition to their classical genomic effects, exert rapid non-genomic actions on cardiomyocytes and vascular cells. These effects are independent of nuclear transcription and can manifest within seconds to minutes, explaining why thyroid hormone–mediated arrhythmias may occur rapidly, even before structural remodeling develops.

Key Non-Genomic Mechanisms

a. PI3K/Akt Pathway Activation

AMERICAN ACADEMIC PUBLISHER
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- T3 stimulates phosphatidylinositol 3-kinase (PI3K), leading to downstream Akt phosphorylation.
- Consequences in cardiomyocytes: Enhanced nitric oxide (NO) production → vasodilation, reduced systemic vascular resistance, increased cardiac preload. Phosphorylation of L-type Ca^{2+} channels → increased Ca^{2+} influx during the plateau phase of the action potential. Modulation of Na^{+}/K^{+}-ATPase activity → faster repolarization and altered intracellular ionic gradients.

Clinically, these changes contribute to acute tachycardia, enhanced cardiac output, and increased susceptibility to atrial ectopy.

b. MAPK (Mitogen-Activated Protein Kinase) Pathway

- Both T3 and T4 can rapidly activate ERK1/2, p38, and JNK pathways in cardiomyocytes.
- Effects: Ion-channel phosphorylation: Modifies open probability and kinetics of L-type Ca^{2+} channels, Kv channels, and RyR2. RyR2 Ca^{2+} leak: Increases spontaneous SR Ca^{2+} release → delayed afterdepolarizations (DADs). Alters gap-junction connexins (Cx43, Cx40) → changes conduction velocity and spatial heterogeneity.

Outcome: increased triggered activity and arrhythmogenic potential, especially in atrial myocardium.

3. Integrin αvβ3–Mediated T4 Signaling

- Unlike T3, T4 can act extracellularly by binding integrin αvβ3 on the plasma membrane.
- Activates Ras–Raf–MAPK signaling.
- Significance: Explains why T4 alone can induce rapid arrhythmic events, even without conversion to T3.

Physiological and Clinical Implications

- Heart Rate: Rapid sinus tachycardia due to increased If current slope and β-adrenergic sensitization.
- Atrial Excitability: Ca^{2+} leak from RyR2 enhances the likelihood of atrial premature contractions and paroxysmal AF.
- Ventricular Excitability: Increased triggered activity can manifest as ventricular ectopy or non-sustained VT in hyperthyroid patients.
- Therapeutic Implication: Non-genomic effects may be partially resistant to β-blockers, highlighting the need for thyroid control as the primary intervention.

3. Disrupted Deiodinase Activity

Thyroid hormone action at the cellular level depends not only on circulating T3/T4 but also on intracellular regulation by deiodinases:

Deiodinase Isoforms and Function

AMERICAN ACADEMIC PUBLISHER
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1. D1 (Type 1):
    - Found mainly in liver, kidney, and thyroid.
    - Converts T4 → T3 (active) or T4 → rT3 (inactive).
    - Regulates systemic T3 availability.
2. D2 (Type 2):
    - Highly expressed in cardiomyocytes and CNS.
    - Converts T4 → T3 locally → ensures tissue-specific thyroid hormone activity.
    - Key for maintaining local cardiac T3 concentration, even when serum T3 is normal.
3. D3 (Type 3):
    - Converts T3 → T2 (inactive) and T4 → reverse T3 (rT3).
    - Upregulated during cardiac stress, ischemia, or inflammation, creating a local hypothyroid state.

Mechanisms of Arrhythmogenesis via Deiodinase Dysregulation

- Subclinical Hyperthyroidism: Increased D2 activity → excessive intracellular T3 → upregulation of ion channels (HCN2/4, Kv1.5, SERCA2a) → enhanced automaticity and shortened APD → AF predisposition.
- Cardiac Stress or Inflammation: D3 upregulation → intracellular T3 deficiency → slowed repolarization, prolonged QT, reduced Ca^{2+} reuptake → bradyarrhythmias, ventricular ectopy.
- Serum–Tissue Discordance: Even when serum T3/T4 levels are normal, local cardiomyocyte thyroid hormone levels may be altered, explaining arrhythmias in "euthyroid" patients.

Clinical Significance

- Subclinical thyroid dysfunction (both hypo- and hyperthyroid) can trigger atrial fibrillation or ventricular arrhythmias without obvious lab abnormalities.
- Highlights the importance of tissue-specific thyroid hormone assessment (via imaging, functional studies, or surrogate biomarkers) in unexplained arrhythmias.
- Therapeutic implication: Normalization of thyroid hormone signaling, rather than just serum correction, is key to arrhythmia prevention.

Electrophysiological Consequences of Thyroid Hormone Dysregulation

1. Effects on Action Potential (AP)

Thyroid hormones profoundly influence the cardiac action potential (AP) by modulating depolarizing and repolarizing ion currents. Alterations in AP morphology underlie the arrhythmogenic potential in both hyper- and hypothyroid states.

Hyperthyroidism

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
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- Increased IKs and IKr currents: Accelerates phase 3 repolarization → shortened action potential duration (APD). This reduces the effective refractory period, facilitating reentry circuits, particularly in atrial tissue.
- Enhanced If current: Upregulates HCN2/HCN4 channels → steeper phase 4 depolarization → sinus tachycardia and ectopic atrial activity.
- Enhanced Na^+/K^+-ATPase activity: Rapid repolarization supports high-frequency firing of atrial and Purkinje fibers.
- Increased SERCA2a expression and activity: Faster SR Ca^{2+} reuptake → augmented lusitropy and higher contractile frequency.
- Clinical Implication: Together, these changes create a substrate for atrial fibrillation (AF), supraventricular tachycardia (SVT), and premature atrial contractions (PACs).

Hypothyroidism

- Reduced repolarizing K^+ currents: Slows phase 3 repolarization → APD prolongation and QT interval prolongation, increasing risk for torsades de pointes.
- Reduced Na^+ channel expression: Slows phase 0 depolarization → conduction velocity is reduced, increasing vulnerability to reentry mechanisms.
- RyR2 Ca^{2+} channel instability: Diastolic Ca^{2+} leak → delayed afterdepolarizations (DADs), especially under sympathetic stimulation.
- Clinical Implication: Predisposition to sinus bradycardia, AV blocks, prolonged QT, and ventricular arrhythmias.

2. Pacemaker Cell Modulation

Thyroid hormones modulate the sinoatrial (SA) node and atrioventricular (AV) node through ionic and receptor-mediated pathways.

Hyperthyroid State

- Upregulation of HCN2/HCN4 channels: Increases If current → faster diastolic depolarization → sinus tachycardia.
- Increased β_1-adrenergic receptor density and cAMP production: Enhances pacemaker slope → increased automaticity.
- Outcome: Heightened susceptibility to atrial ectopy, paroxysmal AF, and supraventricular tachyarrhythmias.

Hypothyroid State

- Blunted HCN expression: Reduced If current → slower phase 4 depolarization → bradycardia.
- Reduced β-adrenergic receptor density: Diminished sympathetic responsiveness → further slowing of pacemaker activity.
- Clinical Manifestation: Predisposition to sinus node dysfunction and AV conduction abnormalities, including first- or second-degree AV block.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
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3. Conduction System Remodeling

Chronic thyroid hormone imbalance induces structural and functional remodeling of the cardiac conduction system:

Hyperthyroidism

- Enhanced Purkinje fiber automaticity: Facilitates rapid conduction and ectopic foci, increasing arrhythmic potential.
- Electrophysiological heterogeneity: Differential shortening of APD in atrial versus ventricular tissue → favors reentry circuits, particularly in atrial tissue.
- Clinical Relevance: Explains higher prevalence of AF, atrial flutter, and supraventricular tachycardias in hyperthyroid patients.

Hypothyroidism

- Interstitial edema and extracellular matrix alterations: Increase tissue resistance → slowed conduction.
- Reduced Na^+ channel expression: Decreases conduction velocity and phase 0 upstroke.
- Reentrant Vulnerability: Slowed conduction combined with heterogeneous repolarization → promotes reentry-mediated arrhythmias, especially in ventricles.
- Clinical Relevance: May manifest as bundle branch blocks, bradyarrhythmias, and pro-arrhythmic QT prolongation.

4. Integrated Electrophysiological Perspective

- Hyperthyroidism: Short APD + enhanced automaticity + conduction heterogeneity → substrate for tachyarrhythmias.
- Hypothyroidism: Prolonged APD + slowed conduction + Ca^{2+} handling defects → substrate for bradyarrhythmias and torsadogenic events.

This integrated view highlights how thyroid hormone dysregulation simultaneously affects ion channel expression, pacemaker activity, and conduction pathways, creating complex arrhythmogenic landscapes that are clinically observed in both overt and subclinical thyroid disorders.

Thyroid hormone dysregulation induces a multi-tiered transformation of the myocardium. Hyperthyroidism creates a substrate with increased automaticity, shortened refractory periods, atrial stretch, and fibrosis—ideal conditions for atrial fibrillation initiation and maintenance. Non-genomic T4 signaling via integrin αvβ3 and MAPK modifies ion-channel behavior within minutes, explaining rapid arrhythmic onset even before structural remodeling. Hypothyroidism, in contrast, predisposes to bradyarrhythmias and malignant ventricular arrhythmias through prolonged APD, reduced ion-pump activity, and myocardial stiffness. Importantly, subclinical states—characterized by normal T3/T4 but abnormal TSH—still produce local myocardial changes due to altered deiodinase activity, demonstrating that thyroid arrhythmogenesis is not strictly dependent on serum hormone levels. This duality highlights why thyroid screening is

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essential in unexplained arrhythmias, recurrent AF, torsades risk assessment, and pre-ablation planning.

Conclusion

Thyroid hormones play a critical and multifaceted role in regulating cardiac electrophysiology, conduction system function, and myocardial structure. Both hyper- and hypothyroid states induce distinct patterns of ion-channel remodeling, pacemaker modulation, and structural alterations, which collectively create a substrate for a wide spectrum of arrhythmias. A detailed understanding of the molecular, genomic, and non-genomic mechanisms by which thyroid hormone dysregulation affects the heart is essential for accurate diagnosis, effective risk stratification, and individualized therapeutic management in patients with thyroid-related arrhythmias. Early recognition and correction of thyroid dysfunction can significantly reduce arrhythmia incidence and improve clinical outcomes.

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