

## Review Article

# Hyperthyroidism and the Heart

CHRISTOS PANAGOULIS, ANTONIOS HALAPAS, EVAGELOS CHARIATIS, POLIXENI DRIVA, EVAGELOS MATSAKAS

*Department of Cardiology, G. Gennimatas General Hospital, Athens, Greece*

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*Address:*

Christos Panagoulis

*Department of Cardiology  
G. Gennimatas General  
Hospital**154 Mesogion Ave.**15127 Athens, Greece**e-mail:*[chpanagoulis@hotmail.com](mailto:chpanagoulis@hotmail.com)

**T**he cardiovascular effects of hyperthyroidism have been described for the last two centuries and are the cornerstone of its diagnosis in clinical practice. Thyroid hormones act on all the organs, but the heart is particularly affected even by small changes in their serum concentrations. This is especially apparent in subclinical hyperthyroidism, which although characterised by normal levels of triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>), alters a number of measurable cardiac parameters.

Hyperthyroidism generally increases heart rate, myocardial contractility, cardiac output, and left ventricular mass, while it predisposes to supraventricular and ventricular arrhythmias. The spectrum of haemodynamic changes and cardiovascular complications that accompany hyperthyroidism reinforces the importance of thyroid hormones in the physiology of the cardiovascular system.

**Molecular and cellular mechanisms involved in the action of thyroid hormones on the heart**

The changes in cardiac parameters that result from hyperthyroidism are due to the action of T<sub>3</sub>. T<sub>3</sub> is the only thyroid hormone that is active at the molecular level and it has genetic and extragenic effects on the myocardium and the blood vessels.<sup>1</sup> The effect of thyroid hormones on the heart is exerted via two mechanisms. The main mechanism is by direct action on the transcrip-

tion of specific and non-specific genes.<sup>2</sup> The second is through non-genomic effects on the plasma membrane, the mitochondria, and the sarcoplasmic reticulum.<sup>3</sup>

Because of their lipophilic nature, T<sub>3</sub> and T<sub>4</sub> pass easily through the cytoplasmic membrane of target organs, including myocardial cells. The conversion of T<sub>4</sub> to T<sub>3</sub> occurs in the cytoplasm of many types of cell, although there are no data to show that this conversion also occurs in myocardial cells. The lipophilic T<sub>3</sub> subsequently enters the nucleus, where it binds to thyroid hormone receptors (THRs), of which only two have been identified.<sup>4</sup> Binding of T<sub>3</sub> to a THR triggers its activation, creating a homo- or heterodimer with the 9-cis-retinoic acid receptor (RXR).<sup>5</sup> The T<sub>3</sub>/THR/THR or T<sub>3</sub>/THR/RXR complex recognises one of the many DNA consensus sequences, which are called thyroid response elements (TREs) and are located in the enhancer region of the target gene.<sup>4</sup> Binding of the protein complex with one of the TREs activates the promoter of the target gene resulting in the initiation of transcription.

In the heart, many genes have been identified that can be targets for the initiation of transcription by thyroid hormones, such as those for alpha-myosin heavy chain fusion (MHC- $\alpha$ ), the sarcoplasmic reticulum calcium pump (SERCA), the cellular membrane Na-K pump (Na-K ATPase), the  $\beta_1$  adrenergic receptor, cardiac troponin I, and atrial natriuretic peptide (ANP).<sup>6-8</sup> Conversely, it has been proved that the tran-

scription of other genes, such as those for beta-myosin heavy chain fusion (MHC- $\beta$ ), adenylic cyclase (IV and V), and the Na-Ca antiporter, is suppressed.<sup>9</sup> In addition, T<sub>3</sub> has direct extragenic actions on the function of the Na, K, and Ca channels of the cellular membrane, thus affecting myocardial and vascular function.

Three MHC isoforms have been found in the myocardium: V<sub>1</sub> composed of MHC- $\alpha/\alpha$ , V<sub>2</sub> of (MHC- $\alpha/\beta$ ), and V<sub>3</sub> of (MHC- $\beta/\beta$ ). Thyroid hormone, via its transcriptional activity on MHC- $\alpha$  and MHC- $\beta$ , displaces the expression of their isoforms, increasing the rate of V<sub>1</sub> synthesis and reducing the rate of V<sub>3</sub> synthesis.<sup>6,9,10</sup> Because of the increased enzymic activity of ATPase, V<sub>1</sub> is characterised by an increase in the speed of myocardial fibre shortening. The effect of thyroid hormones on the genetic expression of MHC improves myocardial contractility.

The contribution of the above mechanism to increased myocardial contractility remains to be proved in humans. A second possible mechanism involves the release and recapture of Ca by the sarcoplasmic reticulum, which controls the rate of contraction and relaxation of myocardial fibres. Thyroid hormone, by promoting SERCA and inhibiting the action of phospholamban at the protein level, accelerates the recapture of Ca by the sarcoplasmic reticulum, increasing peak myocardial tension as well as reducing the duration of ventricular myocardial systole.<sup>7</sup> This mechanism also explains the improvement in diastolic properties, especially relaxation, that are observed in hyperthyroid myocardium. Studies have shown that the stronger inotropic property is due to an increased number of  $\beta$ -adrenergic receptors in the heart along with an increase in their sensitivity to catecholamines, even when the levels of the latter are normal or low.<sup>11</sup> However, recent studies have demonstrated that thyroid hormone does not increase the sensitivity of left ventricular contractility to  $\beta$ -adrenergic receptor stimulation.<sup>12</sup>

In contrast to the genetic effects of thyroid hormone, their non-genomic pathways promote processes with a rapid onset, such as the increased cardiac output that appears after intravenous T<sub>3</sub> administration.<sup>13</sup> Thyroid hormone, via a non-genomic action on the cellular membrane, prolongs the activation of Na channels in myocardial cells<sup>14</sup> and induces intracellular Na uptake and secondary activation of the Na-Ca antiporter, which probably explains thyroid hormone's direct inotropic effect.<sup>3</sup> Also, T<sub>3</sub> exerts a direct effect on L-type Ca channels, causing the entry of Ca into myocardial cells.<sup>15</sup>

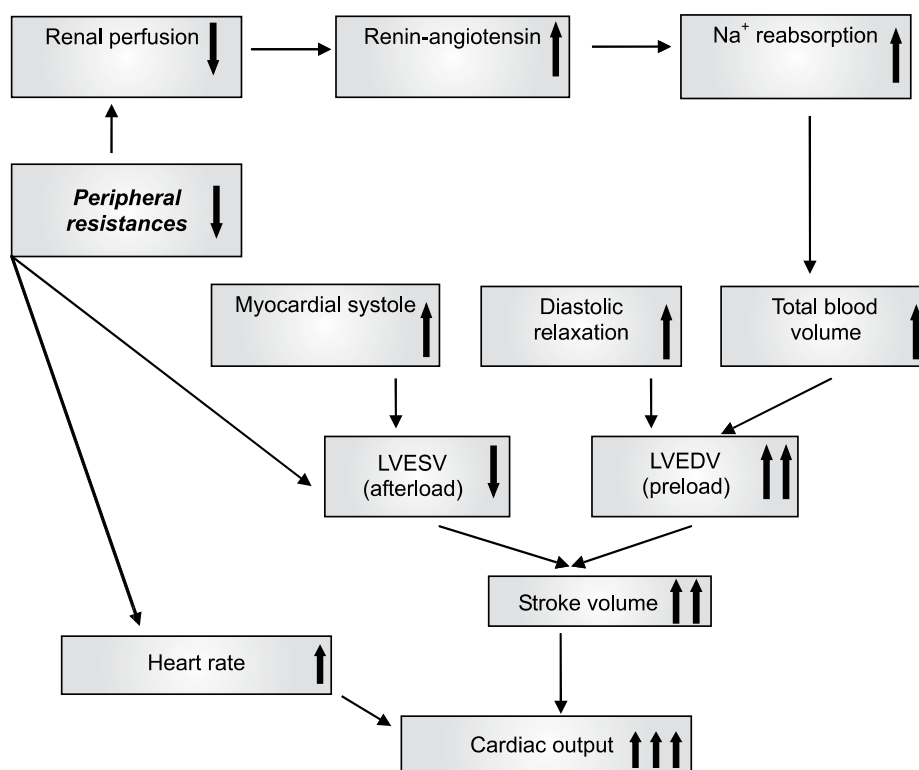
## Haemodynamic consequences of hyperthyroidism

The haemodynamic consequences of hyperthyroidism are due to the direct action of thyroid hormone on the heart and blood vessels (Table 1, Figure 1). Hyperthyroidism is characterised by an increase in resting heart rate, blood volume, stroke volume, myocardial contractility and ejection fraction, and an improvement in diastolic relaxation. The result is an increase in cardiac output of up to 250% and a widening of pulse pressure. In the vasculature, the rapid use of oxygen, increased production of metabolic end-products, and relaxation of arterial smooth muscle fibres by thyroid hormone cause peripheral vasodilation, leading to a reduction in peripheral vascular resistance (PVR).<sup>16</sup> The fall in PVR plays a central role in the haemodynamic changes that accompany hyperthyroidism, contributing to a further increase in heart rate, a selective blood flow increase in certain organs, such as the skin, skeletal muscles and heart, and to a fall in diastolic pressure with a simultaneous widening of pulse pressure. The vasodilation and the absence of an increase in renal blood flow lead to a reduction in renal perfusion and activation of the renin-angiotensin system, which increases Na retention and blood volume.<sup>17,18</sup> The combination of the increase in blood volume and the improvement in the diastolic relaxation phase of cardiac function contributes to an increase in left ventricular end-diastolic volume (LVEDV). The net result of increased preload and reduced afterload is translated into a significant increase in stroke volume. Similarly, the increase in heart rate and stroke volume leads to a doubling or tripling of cardiac output. The cardiac output is much greater than would be expected from the high levels of thyroid hormone and the increase in the body's metabolic rate.<sup>17</sup> Of the preceding factors, the increase in preload is the one mainly responsible for the increase in cardiac output.<sup>19</sup>

The above mentioned changes in systolic and diastolic cardiac function are completely reversed, or at least significantly improved, after the restoration of

**Table 1.** Haemodynamic consequences of hyperthyroidism.

- Peripheral vasodilation.
- Reduction in renal perfusion.
- Reduction in peripheral resistances.
- Increase in myocardial contractility.
- Improvement in diastolic relaxation.
- Increase in heart rate.
- Increase in stroke volume.
- Increase in cardiac output.



**Figure 1.** Schematic representation of the haemodynamic changes that accompany hyperthyroidism. A central role is played by peripheral vascular resistances. LVESV – left ventricular end-systolic volume; LVEDV – left ventricular end-diastolic volume.

thyroid function.<sup>20</sup> This has led to the hypothesis that the dyspnoea on effort and reduced exercise tolerance that accompany hyperthyroidism may not be of cardiac origin. Also, the improvement in diastolic function has not been confirmed by haemodynamic measurements and should be viewed with caution, since the increase in contractility and preload that accompanies hyperthyroidism also affects the echocardiographic indexes of diastolic function (Table 1, Figure 1).

### Cardiac manifestations of hyperthyroidism

The clinical manifestations of hyperthyroidism are characteristic of the multiple actions of thyroid hormones on various target organs (Table 2). Usually, patients with hyperthyroidism develop hyperexcitability, nervousness, emotional instability, muscular weakness, disturbances of menstrual flow, weight loss despite increased food intake, and cardiovascular symptoms, such as palpitations in 85% of patients,

dyspnoea on effort and weakness in about 50% of cases. These symptoms may be mild initially and gradually worsen. The appearance of angina, which may be due either to a disturbance of the oxygen supply/demand equilibrium, or to vasoconstriction, is rare; however, it usually suggests the presence of obstructive coronary artery disease. During the clinical examination the most common finding from the cardiovas-

**Table 2.** Cardiovascular complications of hyperthyroidism.

Symptoms and signs	Incidence (%)
Palpitations	85
Reduced exercise tolerance	65
Dyspnoea on effort	50
Easy tiring	50
Angina on effort	5
Tachycardia	90
Systolic murmur	50
Systolic hypertension	30
Atrial fibrillation	15

cular system is tachycardia, with 90% of patients having a resting heart rate >90 /min.

Most patients have a strong peripheral pulse, wide-spectrum pulse pressure, increased volume of heart sounds, and a systolic ejection murmur in 50% of cases. A systolic sound called Means-Lerman "scratch" murmur is found more rarely, and is due to friction between the pericardium and the pleura, mimicking pericardial rub. In patients with Graves' disease there is an increased incidence of mitral valve prolapse.<sup>21</sup> Recent studies interpret the haemodynamic changes that accompany hyperthyroidism as a cause of this disorder, while the existence of a genetic substrate has been suggested. The presence of a systolic murmur in patients with hyperthyroidism increases the likelihood of the presence of mitral insufficiency as the result of mitral valve prolapse.

### Cardiac complications of hyperthyroidism

Hyperthyroidism may either complicate pre-existing cardiac disease or cause cardiac complications in individuals with a normal myocardium. Because of the increase in heart rate, myocardial contractility, and oxygen demand, hyperthyroidism can also give rise to conditions such as silent coronary artery disease or compensated heart failure.

### Rhythm disturbances

The most common electrocardiographic findings in hyperthyroid patients are sinus tachycardia and shortening of the PR interval. Despite the improvement in atrioventricular conduction, intra-atrial and intraventricular conduction disturbances occasionally result. More frequent is the prolongation of intra-atrial conduction as evidenced by an increase in P-wave duration. Intraventricular conduction delay in the form of right bundle branch block is seen in around 15% of patients, while atrioventricular block may also occur, for reasons unknown. In addition, hyperthyroidism may lead to early atrial systoles, paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter.<sup>22</sup>

Among these arrhythmias, atrial fibrillation is the most common cardiac complication of hyperthyroidism. It occurs in 5-15% of cases and is usually accompanied by a rapid ventricular response. It is more common in men, and its incidence increases significantly with age, while it is rarely found in men aged <40 years.<sup>23</sup> Atrial fibrillation is found in 25% of el-

derly hyperthyroid patients. The majority of patients with hyperthyroidism and atrial fibrillation have an enlarged left atrium, as opposed to 7% of hyperthyroid patients who are in sinus rhythm.<sup>24</sup> As in the case of angina or heart failure, the development of atrial fibrillation should not be attributed solely to the hyperthyroidism, and the patient should undergo investigation for the presence of underlying organic heart disease.

In contrast to atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia are rarely encountered. Ventricular tachycardia, too, is rare, and its presence is suggestive of underlying heart disease.

Patients with subclinical hyperthyroidism also have an increase in mean heart rate over 24 hours and an increase in the number of atrial extrasystoles, as well as a higher incidence of atrial fibrillation. The Framingham study recorded the 10-year prognosis of 2000 patients aged over 60 years who were clinically euthyroid and in sinus rhythm. Of the 61 patients with low levels of thyroid stimulating hormone (TSH) (<0.1 mU/l) 28% developed atrial fibrillation, versus 11% of the 1576 patients with normal levels ( $\geq 0.1$  mU/l). Analysis of the data showed that a low TSH concentration was associated with a tripling of the risk of developing atrial fibrillation. Especially interesting was the fact that overt hyperthyroidism was observed in only two patients with low TSH levels and in one with normal levels. These data agree with those of other studies showing that most patients with low levels of TSH do not develop overt hyperthyroidism.<sup>25</sup> Consequently, the risk of atrial fibrillation in patients with subclinical hyperthyroidism is the same as in patients with clinical hyperthyroidism.

### Heart failure

Haemodynamic compromise due to hyperthyroidism reduces myocardial contractile reserve and impedes the further increase in cardiac output and ejection fraction during exercise, probably because of the inability to reduce the already low PVR. In consequence, the hyperthyroid heart functions at its full capacity even in a resting state. The forced increase in preload and total blood volume increases cardiac work and promotes the development of myocardial hypertrophy, thus allowing the heart to compensate successfully for the haemodynamic burden.<sup>26</sup>

The majority of hyperthyroid patients are in a state of high cardiac output without any symptoms of

heart failure. However, despite the doubling or tripling of cardiac output and above-normal contractility, the increase in both preload and blood volume leads to a rise in ventricular filling pressure and thus to a moderate degree of pulmonary and peripheral congestion. This “high output heart failure” usually appears in patients of young age who have severe and long-term hyperthyroidism in the absence of underlying heart disease, and it responds well to treatment with diuretics.

A small percentage of patients, mainly those who are elderly and have atrial fibrillation or underlying heart disease, develop heart failure with reduced contractility and ejection fraction and increased left ventricular dimensions.<sup>27</sup> This is associated with a widening of the arteriovenous oxygen difference ( $AVO_2$ ), a reduction in cardiac output, a further increase in ventricular filling pressure and PVR, and the presence of a third heart sound. This form of systolic dysfunction is usually reversed when thyroid function is restored.<sup>27,28</sup> The reason why some patients develop “hyperthyroid cardiomyopathy” and advanced heart failure remains unknown.<sup>29</sup> The explanation could be the detrimental effect of sustained tachycardia.<sup>30</sup>

### Hypertension

One third of patients with hyperthyroidism, mainly the elderly, exhibit systolic arterial hypertension. This is due partly to the inability of the vascular system to respond to the increased stroke volume. The reduction in PVR leads to a fall in diastolic pressure, thus explaining the low mean blood pressure and the rare occurrence of diastolic hypertension in these patients.<sup>31</sup> Restoration of thyroid function completely reverses these changes.

### Effect of cardiovascular disturbances and drugs on levels of thyroid hormones

Non-thyroid systemic diseases may cause significant changes in the levels of thyroid hormones in patients without overt thyroid disease. These are usually expressed as low levels of  $T_3$ , or in some cases as a low  $T_3/T_4$  ratio, while TSH levels are normal. Low  $T_3$  levels may be seen in up to 50% of hospitalised patients and in a large number of patients with heart failure or a history of aortocoronary bypass (Table 2).<sup>32</sup>

A number of cardiological medications may affect the levels of thyroid hormones in otherwise euthyroid patients. More than 50% of patients who take amiodarone on a chronic basis show significant changes in thyroid hormone levels, as shown by a 45% increase in  $T_4$  levels while  $T_3$  and TSH levels remain normal.<sup>33</sup> Consequently, an increase in  $T_4$  levels in patients who are taking amiodarone should not automatically be taken as a sign of hyperthyroidism. Since amiodarone causes hyperthyroidism in 2-25% of cases, the interpretation of thyroid hormone levels becomes difficult. The appearance of hyperthyroidism is characterised by an increase in  $T_4$  levels with a simultaneous significant decrease in TSH, while most patients develop clinical manifestations suggesting the overproduction of thyroid hormones. In patients who are taking amiodarone chronically the measurement of TSH is a more reliable index for checking thyroid function.<sup>33</sup>

### Treatment of cardiovascular disease related to hyperthyroidism

In patients who have tachycardia without accompanying cardiac complications such as unstable angina, conservative management with antithyroid medications is mainly indicated. In patients who have tachy-

**Table 3.** Effect of cardiovascular drugs on concentrations of thyroid hormone.

Medication	Mechanism of action	Effect on thyroid hormone concentrations
Amiodarone (iv)	Blocks conversion of $T_4$ to $T_3$	$\uparrow$ TSH, $\uparrow$ $T_4$ , $\downarrow$ $T_3$
Amiodarone (long-term)	Blocks conversion of $T_4$ to $T_3$	$\uparrow$ $T_4$ , $\rightarrow$ $T_3$ and TSH
Furosemide (iv)	Blocks binding of $T_3/T_4$ to TBG	$\downarrow$ $T_4$ , small $\uparrow$ free $T_4$
Heparin (iv)*	Blocks distribution of $T_4$ to tissues	Small $\uparrow$ $T_4$ and free $T_4$
Propranolol	Blocks $T_4$ conversion in periphery	Small $\downarrow$ $T_3$
Propranolol*	Blocks cellular uptake of $T_4$	$\uparrow$ $T_4$ and free $T_4$
Metoprolol/atenolol	No effect	$\rightarrow$ $T_3/T_4$ , $\rightarrow$ TSH
Calcium blockers	Blocks tissue $T_3$ uptake	?
Nicotinic acid	Reduces serum TBG concentrations	$\downarrow$ $T_4$
Dopamine	Inhibits TSH production	$\downarrow$ TSH, $\rightarrow$ $T_3/T_4$

\*In high doses;  $\rightarrow$  no change. TBG – thyroid binding globulin; TSH – thyroid stimulating hormone.

cardia accompanied by unstable angina due to underlying coronary artery disease, coronary vasoconstriction, or thyrotoxicosis, a rapid reduction of heart rate should be sought directly through the use of  $\beta$ -blockers.<sup>34,35</sup> Because of the potential risk, these patients should be monitored haemodynamically in an intensive care unit. The administration of  $\beta$ -blockers limits the  $\beta$ -receptor-mediated symptoms of hyperthyroidism, such as intense anxiety and tremulousness.

The increased plasma clearance in hyperthyroidism usually necessitates higher doses of  $\beta$ -blockers.<sup>36</sup> Among these drugs, propranolol has the advantage that it reduces the conversion of  $T_4$  to  $T_3$  in peripheral tissues; however, this action is of limited therapeutic value, while other cardioselective drugs with a longer half life are equally effective. The release of hormone from the thyroid gland is inhibited by inorganic iodide; thus, these substances are beneficial because of their rapid onset of action. The correction of hyperthyroidism may begin with drugs such as propylthiouracil, which inhibits thyroid hormone synthesis.<sup>37</sup>

In patients whose thyrotoxicosis is accompanied by congestive heart failure, medication with diuretics such as furosemide helps to reverse the volume overload. Digoxin is less beneficial in hyperthyroid than in euthyroid patients because of their relative resistance to its action. This is due in part to its distribution through a greater blood volume and to the need to block more Na-K-ATPase channels in the myocardium.<sup>38</sup> Consequently, even very small doses of digoxin with zero benefit to the myocardium may lead to toxic digitalism. Regardless of the above limitation, digoxin administration should always be a therapeutic solution in patients with heart failure and concomitant atrial fibrillation. B-blockers should be used with caution in patients with heart failure, because of the risk of worsening symptoms; thus, the decision to administer them should be based on the fact that an elevated heart rate contributes to a deterioration of heart failure. Drugs with a short duration of action, such as esmolol, may be given intravenously under monitoring in order to achieve a prompt therapeutic result.<sup>39</sup>

In patients with rapid atrial fibrillation no attempt at electrical cardioversion should be made until thyroid function is restored, since the maintenance of sinus rhythm is impossible as long as the patient is hyperthyroid.<sup>40</sup> The initial therapeutic goal should be to control the ventricular rhythm, usually with a  $\beta$ -blocker. The administration of Ca blockers, such as diltiazem or verapamil, benefits the long-term control of ventricular rate. However, the intravenous administration of Ca

blockers should be avoided, since it may lead to a further fall in PVR and malignant hypotension.<sup>40</sup>

Once the desired level of thyroid hormones has been achieved, the spontaneous restoration of sinus rhythm depends on a number of parameters, such as the patient's age, the duration of atrial fibrillation, the size of the left atrium, and the presence of underlying heart disease. Two thirds of patients with relatively short-duration atrial fibrillation spontaneously convert to sinus rhythm after thyroid hormone levels are restored.<sup>39</sup>

The question of anticoagulant therapy in patients with hyperthyroidism and concomitant atrial fibrillation has not been fully elucidated. In contrast to older studies, recent findings show that patients with hyperthyroidism and atrial fibrillation do not constitute a high-risk group for thromboembolic episodes or cerebrovascular stroke, compared to patients of the same age who have atrial fibrillation of different aetiology. As with other causes of atrial fibrillation, age and the presence of underlying heart disease increase the risk of thromboembolic episodes.<sup>23</sup> Some investigators have reported that anticoagulant administration is not necessary in young patients with short-duration atrial fibrillation (<2-3 months) and without underlying heart disease, in whom restoration of sinus rhythm can be expected soon after the start of antithyroid therapy. In older patients with long-duration atrial fibrillation, and especially in those with underlying heart disease, who are at high risk for a thromboembolic episode, anticoagulant treatment is indicated.<sup>23</sup> Although the recommended dosage of vitamin K antagonist (e.g. acenocoumarol) is the same, hyperthyroid patients need smaller doses than euthyroid patients, because of their faster elimination of vitamin K-dependent clotting factors.<sup>38</sup>

## Conclusions

In recent years there has been significant progress in our understanding of the molecular mechanisms of the cardiac complications of hyperthyroidism. Since the heart is a target organ for many of the genomic and non-genomic effects of thyroid hormone, most patients with hyperthyroidism show haemodynamic and cardiovascular manifestations. The cornerstone of the diagnosis is still the measurement of serum thyroid hormones and TSH.

Since some conditions and cardiovascular medications affect the levels of thyroid hormone, care is required in the diagnosis of thyroid dysfunction. Severe cardiac complications, such as congestive heart

failure, atrial fibrillation, and angina, may appear in hyperthyroid patients and in their treatment priority should be given to controlling the hyperthyroidism.

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