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The Role of Thyroid Hormone in Heart Disease

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Abstract

Thyroid hormone can have an impact on several molecular pathways in both the circulatory system and the heart, either by increasing or decreasing their activity. This can result in the emergence of pertinent cardiovascular diseases. It is widely acknowledged that overt hyperthyroidism can result in a hyperdynamic cardiovascular condition, defined by excessive cardiac output and low systemic vascular resistance. In contrast, overt hypothyroidism is associated with the opposite changes, including an accelerated heart rate, improved function of the left ventricle (LV) during both systole and diastole, and a higher occurrence of supraventricular tachyarrhythmias, such as atrial fibrillation. These modifications are linked to an increased likelihood of developing congestive heart failure. Nevertheless, it remains uncertain whether variations in cardiac function related to evident thyroid disorders are primarily attributable to changes in cardiac workload or irregularities in myocardial contractility. There is a significant amount of research that shows the cardiovascular system responds to the small yet consistent fluctuations in thyroid hormone levels in the bloodstream. These alterations suggest that individuals have subclinical thyroid impairment. Subclinical hyperthyroidism is linked to various negative health consequences,

such as an elevated risk of cardiovascular mortality, an elevated heart rate, atrial arrhythmias, left ventricular hypertrophy, and reduced exercise capacity. Subclinical hypothyroidism is not only linked to a moderate level of dysfunction in the left ventricle's systolic and diastolic functions, but it also increases the likelihood of developing atherosclerosis and experiencing a myocardial infarction. Given that all cardiovascular abnormalities can be reversed by restoring euthyroidism (also referred to as "subclinical hypothyroidism") or reduced by - blockade and L-thyroxine (L-T4) dose adjustment (also known as "subclinical hyperthyroidism"), it is advisable to promptly initiate treatment to prevent any negative impact on the cardiovascular system. It is noteworthy that certain research indicates that patients who have had cardiac surgery, as well as those with acute and chronic cardiovascular issues, may experience changes in the metabolism of peripheral thyroid hormone, potentially impacting heart function. Initial clinical data indicate that individuals suffering from acute and chronic cardiovascular illness may experience substantial advantages from the administration of thyroid hormone or its analogue, 3,5-diiodothyropionic acid. This holds true irrespective of whether the patients are suffering from acute or chronic cardiovascular disease. Considering this information, it seems that administering thyroid hormone might be advantageous in the treatment of these patients.

Keywords: hyperthyroidism, hyperdynamic cardiovascular condition, thyroid disorders, irregularities in myocardial contractility.

Introduction

Klein and Ojamaa (2001) assert that thyroid hormone has a significant influence on the cardiovascular system. The various symptoms and signs seen in individuals with overt hyperthyroidism and hypothyroidism are caused by the distinct impacts of the hormone on the cardiovascular system. Additionally, the resulting hemodynamic abnormalities further contribute to these effects. (Table I)

Subclinical thyroid dysfunction has been demonstrated to impact the circulatory system, potentially elevating the risk of cardiovascular disease. This has become evident in recent years. The relationship between the changes in metabolism caused by thyroid hormone and the impaired circulation resulting from both acute and chronic cardiovascular disease is becoming more evident. This chapter will commence with a succinct summary of the basic mechanisms by which thyroid hormone affects the cardiovascular system and its clinical associations. Subsequently, the chapter will analyze the potential advantages of thyroid hormone therapy for those afflicted with cardiovascular problems.

Cellular Effects of Thyroid Hormone on the Cardiovascular System

The majority of the cellular and molecular pathways underlying the cardiovascular effects of thyroid hormone have been revealed. Based on the depiction in Figure 1, thyroid hormone has the capacity to affect cardiac myocytes through both genomic and nongenomic mechanisms. Dillmann (1990) proposed that the genomic effects of thyroid hormone occur through the activation or suppression of certain target genes that encode proteins with both structural and functional roles. At the start of this process, specialized transport proteins situated in the cell membrane bring Triiodothyronine (T3), the physiologically active thyroid hormone, into the cardiomyocyte (Everts et al., 1996). Everts et al. (1996) have asserted that there is presently no definitive evidence supporting the conversion of thyroxine (T4) to T3 by cardiomyocytes. The importance of this alteration in terms of its impact on the body's functions cannot be emphasized enough. After entering the cardiomyocyte, T3 moves towards the nucleus and interacts with certain nuclear receptors 1 and 2. These receptors have the ability to either inhibit or enhance transcription. When T3 binds to these receptors along with recruited cofactors, the thyroid hormone–receptor complex can either bind (nuclear receptor –1) or release (nuclear receptor –2) specific DNA sequences known as thyroid–responsive elements.

Subsequently, these components act as cis- or trans-regulators, enabling them to modulate the rate of transcription for certain target genes (Brent, 1994).

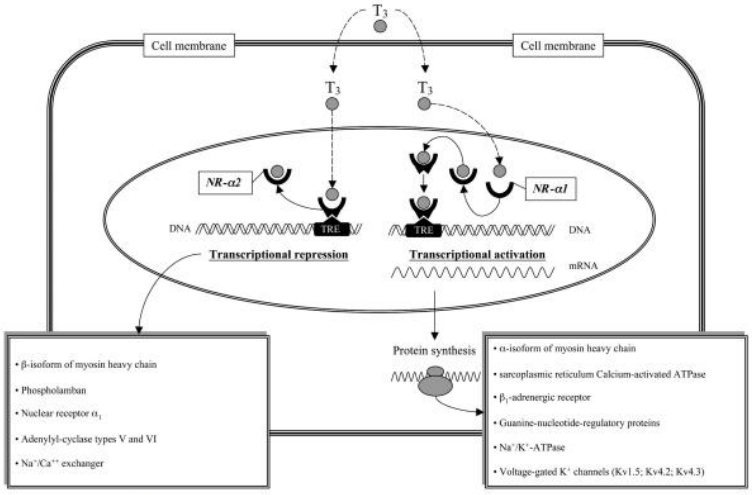

FIG. 1. Genomic effects of thyroid hormone (T3) on cardiomyocytes. NR, triiodothyronine nuclear receptor; TRE, thyroid hormone responsive element (see text for details).

The proteins that have been most extensively studied are the sarcoplasmic reticulum protein responsible for regulating intracellular calcium levels, particularly calcium-activated ATPase and its inhibitory cofactor, phospholamban (Dillmann, 1990; Kiss et al., 1994), and myosin heavy chains (Morkin, 1993; Ojamaa et al., 1996b). Transcriptional regulation governs the expression of these proteins (Figure 1). Several in vitro and experimental rat studies (Morkin, 1993; Ojamaa et al. 1996b) have unequivocally shown that thyroid hormone increases the expression of the -isoform of the myosin heavy chain in cardiomyocytes, while simultaneously decreasing the expression of the - isoform. Ladenson et al. (1992) provide evidence indicating that people are also subject to this regulation. The extent of this phenomenon, however, is undoubtedly less conspicuous in rodents. This conclusion casts doubt on the functional equivalence of the molecular effect. The influence of thyroid hormone on the ratio is minimal, with the -isoform of the myosin heavy chain being more

common in humans than the -isoform (Magner et al., 1988; Ladenson et al., 1992). However, various research studies provide evidence indicating that certain abnormalities in cardiac function among patients with thyroid dysfunction are specifically caused by the impact of thyroid hormone on calcium-activated ATPase and phospholamban. These two components play a crucial role in regulating calcium levels in cardiomyocytes during the systolic phase (Dillmann, 1990; Kiss et al., 1994). This is the case because these enzymes regulate the calcium levels in cardiomyocytes during the systolic portion of the heart rhythm. Sarcoplasmic reticulum calcium-activated ATPase is thought to control the speed at which calcium is taken up into the lumen of the sarcoplasmic reticulum during diastole. This enzyme plays a critical role in determining the speed at which the heart relaxes after contracting (Dillmann, 1990; Kiss et al., 1994). Phospholamban expression levels directly impact the activity of calcium-activated ATPase in the sarcoplasmic reticulum. Kiss et al. (1994) found that an increase in phospholamban expression is associated with a decrease in the activity of calcium-activated ATPase in the sarcoplasmic reticulum. Multiple pieces of evidence have specifically shown that thyroid hormone enhances cardiac relaxation by upregulating the expression of sarcoplasmic reticulum calcium-activated ATPase and downregulating the expression of phospholamban (Dillmann, 1990; Kiss et al., 1994). This specific mechanism is accountable for the improvement of cardiac relaxation. Indeed, the heightened absorption of calcium that takes place during diastole has the capacity to positively impact the heart's contractility. Indeed, the decrease in calcium's concentration inside the cytoplasm towards the end of diastole leads to an elevation in the calcium's systolic transient. Consequently, this elevation enhances the availability of calcium for the activation of tropomyosin units. Phospholambandeficient rats were seen to have heightened cardiac contractility, and this enhancement was reversed upon administration of thyroid hormone (Kiss et al., 1998). The results

of this investigation offer strong evidence for the crucial role that sarcoplasmic reticulum proteins play in the modifications to systolic cardiac performance mediated by thyroid hormone in persons with thyroid disease. These proteins also influence the balance of calcium within the cell. It is crucial to understand that thyroid hormone can affect the development of many ion channels, including voltage-gated K channels (Kv1.5, Kv4.2, and Kv4.3), Na/Ke-activated ATPase, and the Na/Ca_{+} exchanger, in this particular situation. This contribution functions to control the mechanical and electrochemical reactions that take place in the myocardium, as stated by Gick et al. (1990) and Ojamaa et al. (1999). Thyroid hormone not only impacts the genome, but it also has the capacity to alter the inotropism and chronotropism of the heart more rapidly than expected, considering its role in regulating gene expression. The manifestation of these alterations in phenotype and function often requires a variable timeframe ranging from minutes to many hours. As a result, this leads to inquiries on the role of nongenomic pathways (Walker et al., 1994; Davis and Davis, 1993). Research indicates that thyroid hormone stimulates the phosphorylation of phospholamban, leading to a decrease in the inhibitory effect of phospholamban on calcium-activated ATPase in the sarcoplasmic reticulum (Ojamaa et al., 2002). The activation of intracellular kinase pathways involved in signal transduction of the adrenergic stimulus (Ojamaa et al., 2002) partially mediates this process. This may explain the functional similarities observed between the effects of thyroid hormone on the cardiovascular system and those of the adrenergic system (Levey and Klein, 1990). This is a fascinating observation. The responsiveness of the cardiovascular system to adrenergic stimulation does not seem to be significantly changed in hyperthyroidism or hypothyroidism, even though most of the cardiovascular symptoms associated with these conditions resemble those of increased and decreased adrenergic activity, respectively (Hoit et al., 1997; Ojamaa et al., 2000). Thyroid hormone exerts a substantial influence on the

cardiovascular system, making it a key contributing component. It achieves this by inducing the relaxation of smooth muscle cells in the vascular system, leading to a significant decrease in peripheral vascular resistance (Klemperer et al., 1995; Ojamaa et al., 1996a; Park et al., 1997). According to a study conducted by Napoli et al. in 2001, prolonged excessive levels of thyroid hormone enhance both endothelium-dependent and -independent processes, resulting in significant effects on the body's vascular reactivity.

Overt Hyperthyroidism

According to Nordyke et al. (1988), palpitations are a prevalent sign of overt hyperthyroidism. Based on continuous, ambulatory, 24-hour electrocardiogram (ECG) monitoring conducted by von Olshausen et al. (1989) and Cavaciatori et al. (1996), it has been observed that the heart rate often increases over the day and is further enhanced in response to physical activity. This holds true even if the pulse rate remains relatively constant throughout the day. The examination of the heart rate variability indicates a proportionate rise in sympathetic activity together with an imbalanced interaction between the sympathetic and vagal systems (Cacciatori et al., 1996).

When examining this factor, it is important to observe that persons with overt hyperthyroidism still experience somewhat elevated heart rates, even though β-adrenergic inhibition typically reduces rapid heart rate in these patients compared to individuals with normal thyroid function. Sun et al. (2001) found evidence that supports the concept that thyroid hormone can directly modify the firing of sinus nodes. Sawin et al. (1994) and Auer et al. (2001) discovered that a small percentage, ranging from 5 to 10 percent, of individuals with overt hyperthyroidism may exhibit signs of atrial fibrillation as their first symptom. Once euthyroidism is achieved, atrial fibrillation usually reverts to sinus rhythm (Nakazawa et al., 1982). The rate of reversal diminishes with increasing age and the duration of the arrhythmia (Nakazawa et al., 1982; Nordyke et al., 1988).

This is a frequently reported occurrence. Therefore, the main approach for managing atrial fibrillation associated with overt hyperthyroidism should be to achieve a euthyroid state. The ventricular rate can be efficiently regulated by decreasing β-adrenergic activity. After achieving euthyroidism, it is advisable to explore electrical or pharmaceutical cardioversion as a final option. Nevertheless, there is ongoing debate regarding the appropriateness of administering anticoagulant medication in this particular situation for persons who exhibit visible signs of hyperthyroidism and simultaneously have atrial fibrillation. When using anticoagulant medication, it is important to consider the potential for bleeding in comparison to the danger of systemic embolization. The decision should be made based on the unique circumstances of each patient (Gilligan et al., 1996). Petersen and Hansen (1988) and Gilligan et al. (1996) recommend the regular administration of anticoagulant drugs to older patients with diagnosed or suspected heart disease, as well as those who have been experiencing atrial fibrillation for a prolonged period.

According to the studies conducted by Graettinger et al. (1959), Theilen and Wilson (1967), and DeGroot and Leonard (1970), individuals with overt hyperthyroidism consistently have elevated systolic arterial pressure and reduced diastolic arterial pressure. This leads to a pulse pressure that is typically broader and only a minor reduction in mean arterial pressure. The fundamental hyperdynamic cardiovascular condition is caused by these hemodynamic anomalies, characterized by a substantial decrease in peripheral vascular resistance and a remarkable increase in cardiac output (Graettinger et al., 1959; Theilen and Wilson, 1967; DeGroot and Leonard, 1970). These alterations are thought to be the underlying factor of the disorder.

Patients with overt hyperthyroidism typically exhibit elevated left ventricular (LV) performance during periods of rest (Biondi et al., 2002a). Nevertheless, the specific factors that play the most essential role in this occurrence remain

unidentified. Biondi et al. (2002a) found that the high cardiac output state is a result of a substantially elevated heart rate and a somewhat augmented stroke volume. This syndrome is subsequently linked to normal or slightly diminished left ventricular end-systolic and end-diastolic dimensions, respectively. Biondi et al. (2002a) found that patients with obvious hyperthyroidism often show an elevation in left ventricular ejection fraction, a metric that assesses the performance of the entire systolic chamber. The exact cause of this process is uncertain, as it is unclear whether it is primarily due to a combination of hemodynamic variables or a true enhancement in the contractility of the myocardium (Biondi et al., 2002a). An illustration of the dispute surrounding this claim can be seen in the studies conducted by Feldman et al. in 1986 and Merillon et al. in 1981. Thirty-six Obtained from the official website of the University of Napoli, namely rphr.endojournals.org. Federico, FAZIO SERAFINO, and their colleagues.

Merillon et al. (1981) examined the left ventricular function of seven persons who were clearly experiencing thyrotoxicosis. They compared these individuals to eleven euthyroid controls who were paced at a similar heart rate. The assessment was conducted via cardiac catheterization. The researchers noted that there were no disparities in the contractile performance parameters between the two groups. The metrics assessed were the left ventricular ejection fraction, the ratio of left ventricular end-systolic pressure to end-systolic volume, the velocity of circumferential fiber shortening, and the rate of rise of left ventricular pressure as a proportion of the total pressure. Researchers found a notable increase in average aortic pressure and systemic vascular resistance associated with atrial pacing, along with a significant decrease in both end-diastolic volume and pressure. Nevertheless, there was no identified correlation between hyperthyroidism and atrial pacing. As expected, the people who were arranged in alphabetical order did not observe a rise in their heart rate. Although atrial

pacing and hyperthyroidism are not exactly the same (one being an acute condition and the other a chronic illness), the authors concluded that there was no significant increase in the actual level of cardiac contractility, independent of changes in heart rate and preload, in human hyperthyroidism. The writers arrived at this conclusion.

Feldman and colleagues (1986) employed echocardiography to examine the left ventricular function in two groups: eleven hyperthyroid patients and eleven age-matched normal people. Based on the researchers' findings, there were no discernible distinctions between the two groups in terms of either the end-systolic meridional wall stress or the end-diastolic width of the left ventricle. In contrast, individuals with hyperthyroidism demonstrated significantly elevated rate-corrected mean velocities of circumferential fiber shortening. This is a metric used to assess the efficiency of the left ventricle (LV) that is designed to be unaffected by the amount of blood filling the heart and the speed at which the heart beats. Consequently, when comparing the LV end-systolic wall stress to the rate-corrected velocity of fiber shortening, it was shown that the values of hyperthyroid patients exceeded the average regression line for individuals with normal thyroid function. This suggests the presence of an elevated contractile state. Although the patients had a higher heart rate, the investigators did not believe that the normal end-diastolic dimension was linked to a significant increase in preload. This was because the researchers also took into account the negative correlation between the two factors. Moreover, the noninvasive technique for assessing cardiac contractility can exaggerate myocardial function in pathological conditions where there are simultaneous increases in preload and heart rate. The reason for this is that the approach establishes a connection between the velocity of circumferential fiber-shortening, adjusted for rate, and the meridional wall tension at end-systole of the left ventricle.

These studies indicate that the higher heart rate observed in individuals with

hyperthyroidism masks the true increase in cardiac preload, leading to an underestimation of the extent to which the Frank-Starling mechanism enhances cardiac function (Biondi et al., 2002a). Indeed, there exists a link between overt hyperthyroidism and an elevation in the preload experienced by the heart. Studies (Gibson and Harris, 1939; Anthonisen et al., 1960) have shown that patients diagnosed with overt hyperthyroidism exhibit an elevated blood volume. Additional investigations (Resnick and Laragh, 1982) have observed activation of the renin-angiotensin-aldosterone pathway in patients with hyperthyroidism. Moreover, it has been determined that thyroid hormone has the capacity to elevate the size of red blood cells and the synthesis of erythropoietin, which may perhaps account for the augmentation in overall blood volume (Gibson). The article "The Cardiac Vascular System and Thyroxine Hormone T 37" was authored by Harris (1939), Graettinger et al. (1959), and Klein and Levey (1984). It was sourced from the website rphr.endojournals.org of the University of Naples Federico II Dip Fisiologi. In addition, numerous studies consistently show that left ventricular diastolic function is improved, with increased indices of early left ventricular filling and faster left ventricular relaxation, regardless of the impact of heart rate (Lewis et al., 1979; Friedman et al., 1982; Mehltz et al., 1991; Kahaly et al., 1999). This diastolic function pattern indicates that enhancing diastolic performance would enable handling a greater venous return without necessitating significant modifications to the filling pressure. Furthermore, it aligns with a greater venous return and an augmented ventricular suction. (Merillon et al., 1981) discovered that hyperthyroid patients and normal individuals exhibited similar measurements for left ventricular end-diastolic volume and pressure. These findings provide evidence in support of this idea. Instead of relying on its inotropic reserve, it is possible that the hyperthyroid heart improves its performance by effectively regulating hemodynamic stressors (Biondi et al., 2002a). This is a potentiality. In this context, it is crucial to

emphasize that actions that utilize cardiac contractility result in a progressively increasing metabolic burden on the heart. This is because the heart is involved in the physiological processes. Using hemodynamic stresses to enhance heart function is a beneficial practice from an energy perspective. Indeed, employing the latter method optimizes the utilization of the heart's mechanical and energetic resources in a situation like hyperthyroidism, when there is already a noticeable increase in the amount of energy being spent by the myocardium (Bengel et al., 2000).

The complicated and nuanced interaction between several factors influencing heart function in patients with overt hyperthyroidism may partially explain two clinical facts. An initial symptom is a decrease in the ability to tolerate physical exercise, which occurs with more frequency (Kahaly et al., 1998, 1999). Congestive heart failure (CHF) development has become less prevalent compared to the past (Magner et al., 1988). Both of these modifications are linked to a heightened susceptibility to cardiovascular disease. Kahaly et al. (1998, 1999) propose that a reduced cardiovascular capacity may be a contributing factor to the reduced exercise tolerance observed in hyperthyroid patients. Indeed, the cardiovascular system utilizes nearly identical pathways during periods of rest and physical exercise. However, it is possible for atrial fibrillation to occur after congestive heart failure (CHF). A potential consequence of a reduced time for diastole and the lack of the atrial contribution to filling the ventricles is a significant disruption in the dynamics of diastole. This disruption can result in an elevation of the pressure at the end of diastole and promote congestion in the body's systems. In various situations, CHF may express itself as

Subclinical Hyperthyroidism

Subnormal or suppressed blood levels of thyroid-stimulating hormone (TSH) indicate the presence of subclinical hyperthyroidism (Biondi et al., 2002c). This refers to the situation where the levels of thyroid hormones in the bloodstream

are within the normal range for the average population. The cause of subclinical hyperthyroidism can be either the result of using suppressive or replacement L-thyroxine medication (exogenous subclinical hyperthyroidism) or due to a disorder within the thyroid gland itself (endogenous subclinical hyperthyroidism) (Biondi et al., 2002c). Biondi et al.'s 2002c study found that the illness called exogenous subclinical hyperthyroidism is more commonly diagnosed in clinical practice. In recent decades, multiple research have been carried out to examine the impact of subclinical hyperthyroidism on cardiac health. Research findings suggest that this condition may be linked to significant abnormalities in the structure and function of the heart (Biondi et al., 2002c). The most prevalent abnormalities observed in patients with subclinical hyperthyroidism include an elevated heart rate, a higher occurrence of supraventricular arrhythmias, and an increased left ventricular mass (Biondi et al., 1993,1994,1996,1999b,2000; Fazio et al., 1995; Ching et al., 1996; Shapiro et al., 1997; Mercuro et al., 2000). The second characteristic is typically linked to a reduction in the ability of the heart to relax, resulting in a slower relaxation of the heart. This is often accompanied by a moderate increase in the ability of the heart to contract (Biondi et al., 1993, 1994, 1996, 1999b, 2000; Fazio et al., 1995; Ching et al., 1996; Shapiro et al., 1997; Mercuro et al., 2000). Concentric remodeling is the word used to describe the growth in mass of the left ventricle without any changes in the dimensions of the cavity, while the thickness of the wall rises. It is not associated with the quantities of thyroid hormone present in the bloodstream, but rather with the length of time subclinical hyperthyroidism persists. It is uncommon for it to be associated with left ventricular hypothyroidism. There is still much to discover about the process underlying the increase in LV mass. The syndrome is typically attributed to a mildly hyperkinetic cardiovascular disease that causes a prolonged hemodynamic overload (Klein, 1988; Fazio et al., 1995). Indeed, individuals with subclinical hyperthyroidism have an augmentation in left ventricular mass, which is linked

to insufficient ventricular filling and reduced myocardial relaxation. This parallels the characteristics reported in conventional models of overload-induced cardiac hypertrophy. It has been suggested that this diastolic dysfunction is caused by changes in how calcium is managed within the cells, resulting from reduced levels of sarcoplasmic reticulum calcium ATPase and/or increased levels of phospholamban. The delayed sarcoplasmic absorption of calcium is most likely to be the cause of the problem. However, this perspective contradicts the documented impact of thyroid hormone on these genes, as demonstrated by Dillmann (1990) and Kiss et al. (1994).

Thus, it is reasonable to propose that the long-term impact of a consistently high cardiac workload on calcium metabolism would be more substantial compared to the effects caused by thyroid hormone. Nevertheless, if euthyroidism is attained, the morphological and functional inadequacies of the left ventricle promptly revert to their normal state. Furthermore, the administration of medications that inhibit the -blocking receptors can effectively ameliorate these abnormalities, as demonstrated by Biondi et al. in their studies conducted in 1994, 1995, 1999b, and 2000. This assumption assigns greater significance to the functional processes that define cardiac involvement in subclinical hyperthyroidism and suggests that it can be reversed.

Significantly, there is ample data indicating that the existence of subclinical hyperthyroidism is linked to a heightened risk of cardiovascular-related mortality (Parle et al., 2001). Although the specific mechanism behind this association has not been determined, it is likely that numerous factors contribute to this phenomena (Biondi et al., 2002b). People with subclinical hyperthyroidism are more susceptible to developing atrial fibrillation, a condition that can raise the risk of thromboembolic events (Petersen and Hansen, 1988; Ladenson, 1993; Sawin et al., 1994; Auer et al., 2001). Consequently, this can increase individuals' vulnerability to atrial fibrillation. Elderly individuals face a substantially higher

risk for this. Studies have demonstrated a connection between a higher heart rate and an increased risk of sudden death, as well as an increase in left ventricular (LV) mass, even when there is no apparent LV hypertrophy (Haider et al., 1998; Greenland et al., 1999). This association persists even in the absence of apparent left ventricular enlargement. Furthermore, it is widely known that the onset of more severe left ventricular failure can be preceded by diastolic dysfunction. Older patients may experience an accelerated onset of congestive heart failure and cardiac decompensation. Biondi et al.'s 2002c research suggests that all patients with benign thyroid disease should either avoid or treat subclinical hyperthyroidism during their treatment. Alternatively, in cases where subclinical hyperthyroidism is being used as a therapeutic measure, such as in patients with differentiated thyroid cancer, it is recommended to use the minimum dosage of L-T4 necessary to achieve a stable suppression of TSH levels, which is ultimately associated with chronic blockade (Biondi et al., 2002c). This is the recommendation proposed by Biondi et al. In this context, individuals with a previous medical record of atrial fibrillation should be considered as potential cases of subclinical hyperthyroidism. This particularly applies to individuals who are advanced in age or have pre-existing heart conditions and report experiencing worsening angina pectoris or cardiac decompensation.

Overt Hypothyroidism

One group of cardiovascular impacts is attributed to an abundance of thyroid hormone, while another group of repercussions is linked to a deficiency of thyroid hormone. However, most individuals do not show any symptoms or signs, and the clear clinical presentation of obvious hypothyroidism is not easily noticeable (Klein and Ojamaa, 2000). The most frequent outcomes observed in individuals with overt hypothyroidism are bradycardia and systemic

hypertension. Additionally, these patients often experience a narrow pulse pressure, a slightly increased mean arterial pressure, and some level of impairment in physical activity (McAllister et al., 1995; Klein and Ojamaa, 2000). These sensations are accompanied by a marginally elevated mean arterial pressure. Individuals with overt hypothyroidism can exhibit abnormalities in their routine ECG. For instance, the T wave may have a flattened or inverted shape, whereas the QT interval may experience an elongation (Fredlund and Olsson, 1983; Klein and Ojamaa, 2000). These anomalies are distinguished by the existence of irregularities. As per Ojamaa et al. (1999), these irregularities indicate that the duration of the ventricular action potential is prolonged. Moreover, persons with overt hypothyroidism have a higher likelihood of experiencing ventricular arrhythmias, especially when they also have ischemic heart illness (Fredlund and Olsson, 1983; Klein and Ojamaa, 2000). This is due to the heightened electrical dispersion that takes place within the myocardium. People with overt hyperthyroidism have a significantly higher prevalence of systemic hypertension compared to those who have normal thyroid function, with the former being roughly three times more likely to develop hypertension. Moreover, there is evidence to suggest that overt hypothyroidism is linked to elevated blood pressure in individuals with systemic hypertension (Endo et al.,

1979; Saito et al., 1983; Streeten et al., 1988; Klein, 1989; Fletcher and Weetman, 1998; Fommei and Iervasi, 2002). Two causes that can cause systemic hypertension in patients with overt hypothyroidism exist. Klein and Ojamaa (2000) state that the first notable change is the substantial rise in peripheral vascular resistance, which is the most widely recognized among the three. Dernellis and Panaretou (2002) and Obuobie et al. (2002) have identified a second phenomena, namely the rise in arterial stiffness, which is believed to be mostly due to arterial wall myxedema. This phenomena has been noticed in more recent times. Traditional therapies sometimes have a restricted capacity to manage systemic hypertension linked to obvious hypothyroidism. However, the situation improves quickly after euthyroidism is attained (Dernellis and Panaretou, 2002). The results of this study would support the idea of regularly assessing thyroid function in all patients with systemic hypertension before diagnosis, especially those who do not show significant improvement with treatment.

The most common cardiac defect found in persons with overt hypothyroidism is impairment in left ventricular diastolic function. This is characterized by delayed myocardial relaxation and poor early ventricular filling (Crowley et al., 1977; Wieshammer et al., 1989). This is the prevailing heart anomaly. LV systolic

function often exhibits just a modest decrease, as seen by somewhat lower values of ejection fraction and stroke volume (Crowley et al., 1977; Wieshammer et al., 1989). This is demonstrated by values that are slightly lower. An explanation for a below-normal cardiac output in overt hypothyroidism can be attributed to the combination of reduced cardiac preload, bradycardia, and slightly decreased myocardial contractility (Crowley et al., 1977; Wieshammer et al., 1989). This is one of the methods that researchers have employed in an effort to elucidate the phenomena. Conversely, reduced ability to exercise in individuals with overt hypothyroidism may be due to impairments in both proximal and peripheral vascular function, as well as a decrease in heart performance (McAllister et al., 1995).

Ladenson et al. (1992) found that severe and persistent overt hypothyroidism can lead to the formation of periodic pericardial effusion, which can occasionally impede heart function. There is a potential correlation between overt hypothyroidism and an enlargement of the left ventricle. However, necropsy and ultrasound studies have demonstrated that the observed increase in left ventricle mass is not caused by strict ventricular hypertrophy, but rather by interstitial myxedema (Aber, 1964). Myxedema of the heart can exacerbate left ventricular mechanics and decrease cardiac output by causing fibrosis in the cardiovascular

system. While overt hypothyroidism is linked to a reduction in the demand for oxygen in the heart, it is important to note that the efficiency of mechanical work in the heart is poorer in hypothyroid individuals. However, this efficiency improves when they achieve a state of normal thyroid function (Bengel et al., 2000). It is imperative to always bear this in mind. Enhanced cardiac afterload, caused by increased arterial stiffness and peripheral vascular resistance in overt hypothyroidism, is a major contributor to the increase in myocardial oxygen demand (Bengel et al., 2000). This variable is one of the most significant factors that impact myocardial oxygen utilization. Keating et al. (1960) found that patients with ischemic heart disease, whether suspected or diagnosed, may experience worsening or triggering of angina due to overt hypothyroidism. In addition, with the initiation of thyroid hormone replacement therapy, certain individuals may experience amelioration of their anginal symptoms. This is likely due to an excessive increase in the amount of oxygen that the myocardium absorbs compared to the level of cardiac function.

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