Effects of Thyroid Hormone on the Cardiovascular System

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ABSTRACT

Increased or reduced action of thyroid hormone on certain molecular pathways in the heart and vasculature causes relevant cardiovascular derangements. It is well established that overt hyperthyroidism induces a hyperdynamic cardiovascular state (high cardiac output with low systemic vascular resistance), which is associated with a faster heart rate, enhanced left ventricular (LV) systolic and diastolic function, and increased prevalence of supraventricular tachyarrhythmias — namely, atrial fibrillation — whereas overt hypothyroidism is characterized by the opposite changes. However, whether changes in cardiac performance associated with overt thyroid dysfunction are due mainly to alterations of myocardial contractility or to loading conditions remains unclear. Extensive evidence indicates that the cardiovascular system responds to the minimal but persistent changes in circulating thyroid hormone levels, which are typical of individuals with subclinical thyroid dysfunction. Subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased LV mass, impaired ventricular relaxation, reduced exercise performance, and increased risk of cardiovascular mortality. Subclinical hypothyroidism is associated with impaired LV diastolic function and subtle systolic dysfunction and an enhanced risk for atherosclerosis and myocardial infarction. Because all cardiovascular abnormalities are reversed by restoration of euthyroidism ("subclinical hypothyroidism") or blunted by β-blockade and L-thyroxine (L-T4) dose tailoring ("subclinical hyperthyroidism"), timely treatment is advisable in an attempt to avoid adverse cardiovascular effects. Interestingly, some data indicate that patients with acute and chronic cardiovascular disorders and those undergoing cardiac surgery may have altered peripheral thyroid hormone metabolism that, in turn, may contribute to altered cardiac function. Preliminary clinical investigations suggest that administration of thyroid hormone or its analogue 3,5-diiodothyropropionic acid greatly benefits these patients, highlighting the potential role of thyroid hormone treatment in patients with acute and chronic cardiovascular disease.

I. Introduction

Thyroid hormone has relevant effects on the cardiovascular system (Klein and Ojamaa, 2001). Many symptoms and signs recognized in patients with overt hyperthyroidism and hypothyroidism are due to the increased or reduced action of thyroid hormone on the heart and the vascular system, respectively, and the related hemodynamic derangements (Table I). In recent decades, it has emerged

TABLE I
Hemodynamics and Cardiac Function in Overt Thyroid Dysfunction

Parameter	Normal values	Hyperthyroidism	Hypothyroidism
Blood volume (% of normal value)	100	105.5	84.5
Heart rate (bpm)	72–84	88–130	60–80
Cardiac output (L/min)	4.0–6.0	$>$ 7.0	$<$ 4.5
Systemic vascular resistance (dyn·sec/cm^{-5})	1500–1700	700–1200	2100–2700
Left ventricular ejection fraction (%)	$>$ 50	$>$ 65	$\leq$ 60
Isovolumic relaxation time (msec)	60–80	25–40	$>$ 80

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that subclinical thyroid dysfunction may affect the cardiovascular system, which may increase cardiovascular risk. It is becoming increasingly apparent that acute and chronic cardiovascular disease may alter thyroid hormone metabolism and contribute to cardiovascular impairment. This chapter will provide an overview of the basic mechanisms underlying the effects of thyroid hormone on the cardiovascular system and their clinical correlates, then address the potential benefit of thyroid hormone treatment in patients with cardiovascular disorders.

II. Cellular Effects of Thyroid Hormone on the Cardiovascular System

Most of the molecular and cellular mechanisms responsible for the cardiovascular effects of thyroid hormone have been clarified. As shown in Figure 1, thyroid hormone may exert both genomic and nongenomic effects on cardiac myocytes. The genomic effects of thyroid hormone are mediated by the transcriptional activation or repression of specific target genes that encode both structural and functional proteins (Dillmann, 1990). This process begins with the entry of triiodothyronine (T3), the biologically active thyroid hormone, into the cardiomyocyte through specific transport proteins located within the cell membrane (Everts *et al.*, 1996). To date, there is no clear evidence of a biologically relevant conversion of thyroxine (T4) to T3 in cardiomyocytes (Everts *et al.*, 1996). Once in the cardiomyocyte, T3 enters the nucleus and interacts with

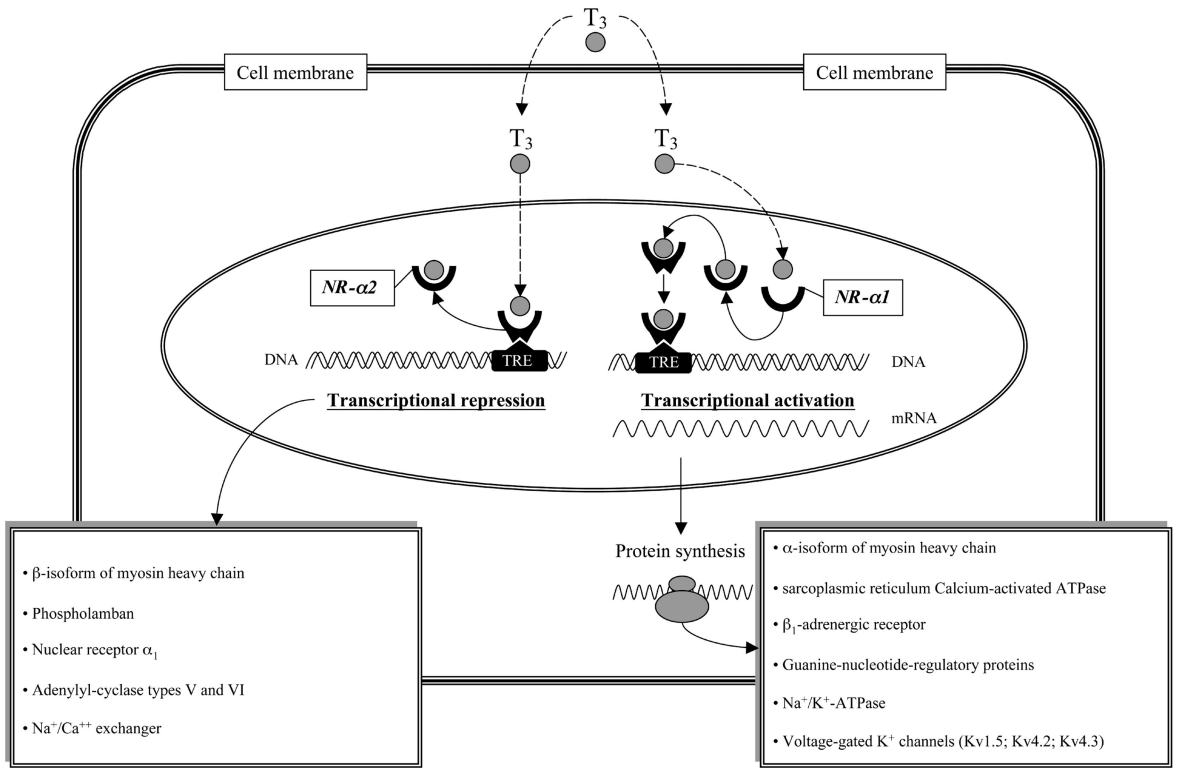

FIG. 1. Genomic effects of thyroid hormone (T3) on cardiomyocytes. NR, triiodothyronine nuclear receptor; TRE, thyroid hormone responsive element (see text for details).

specific transcriptional activators (nuclear receptor α1) or repressors (nuclear receptor α2). Occupancy of these receptors by T3, in combination with recruited cofactors, allows the thyroid hormone-receptor complex to bind (nuclear receptor α-1) or release (nuclear receptor α-2) specific sequences of DNA (thyroid-responsive elements) that, in turn, by acting as cis- or trans-regulators, modify the rate of transcription of specific target genes (Brent, 1994).

Among various proteins whose expression is modulated at transcriptional level (Figure 1), the most-extensively characterized are myosin heavy chains (Morkin, 1993; Ojamaa *et al.*, 1996b) and the sarcoplasmic reticulum protein involved in the regulation of intracellular calcium handling, namely, calcium-activated ATPase and its inhibitory cofactor, phospholamban (Dillmann, 1990; Kiss *et al.*, 1994). Many studies *in vitro* and in experimental rats incontrovertibly show that thyroid hormone upregulates the expression of the α-isoform of the myosin heavy chain in cardiomyocytes, while it downregulates the β-isoform (Morkin, 1993; Ojamaa *et al.* 1996b). There is some evidence that this regulation also occurs in humans (Ladenson *et al.*, 1992). However, the magnitude of this phenomenon is certainly less pronounced than in rodents — a finding that fuels uncertainties about the functional correlate of this molecular effect. In humans, the β-isoform of the myosin heavy chain is more prevalent than the α-isoform (Magner *et al.*, 1988; Ladenson *et al.*, 1992) and the ratio is only marginally modified by thyroid hormone (Ladenson *et al.*, 1992).

In contrast, several lines of evidence suggest that some abnormalities of cardiac function in patients with thyroid dysfunction directly reflect the effects of thyroid hormone on calcium-activated ATPase and phospholamban, which are involved primarily in the regulation of systodiastolic calcium concentrations in cardiomyocytes (Dillmann, 1990; Kiss *et al.*, 1994). Sarcoplasmic reticulum calcium-activated ATPase is responsible for the rate of calcium reuptake into the lumen of the sarcoplasmic reticulum during diastole that, in turn, is a major determinant of the velocity of myocardial relaxation after contraction (Dillmann, 1990; Kiss *et al.*, 1994). However, the performance of sarcoplasmic reticulum calcium-activated ATPase is influenced by the level of expression of phospholamban: the higher the phospholamban expression, the lower the sarcoplasmic reticulum calcium-activated ATPase activity (Kiss *et al.*, 1994). In this regard, it has been extensively demonstrated that thyroid hormone upregulates expression of the sarcoplasmic reticulum calcium-activated ATPase and downregulates expression of phospholamban, thereby enhancing myocardial relaxation (Dillmann, 1990; Kiss *et al.*, 1994). Indeed, the improved calcium reuptake during diastole may favorably affect myocardial contractility. In fact, the greater reduction in cytoplasmatic concentration of calcium at end-diastole increases the magnitude of the systolic transient of calcium that, in turn, augments its availability for activation of tropo-myosin units. In fact, in phospholamban-deficient mice, cardiac contractility was found to be increased, with no further

increase after thyroid hormone treatment (Kiss *et al.*, 1998). This finding strongly supports the key role of sarcoplasmic reticulum proteins and their effects on intracellular calcium handling in thyroid hormone-mediated changes in systo-diastolic cardiac function in patients with thyroid dysfunction. In this context, it is important to recognize that thyroid hormone also modifies the expression of other ion channels, such as Na^+/K^+-activated ATPase, Na^+/Ca^{++} exchanger, and some voltage-gated K^+ channels (Kv1.5, Kv4.2, Kv4.3), thereby coordinating the electrochemical and mechanical responses of the myocardium (Gick *et al.*, 1990; Ojamaa *et al.*, 1999).

In addition to these genomic effects, thyroid hormone produces changes in cardiac inotropism and chronotropism more rapidly than would be expected from regulation of gene expression, which usually take minutes to hours to be phenotypically and functionally appreciable. This calls into question the involvement of nongenomic mechanisms (Davis and Davis, 1993; Walker *et al.*, 1994). Some evidence indicates that thyroid hormone promotes the acute phosphorylation of phospholamban and that this action attenuates the inhibitory effect of phospholamban on sarcoplasmic reticulum calcium-activated ATPase (Ojamaa *et al.*, 2002). Interestingly, the fact that this process is mediated at least in part by the activation of intracellular kinase pathways involved in signal transduction of the adrenergic stimulus (Ojamaa *et al.*, 2002) may help to explain functional analogies between the cardiovascular effects of thyroid hormone and those promoted by the adrenergic system (Levey and Klein, 1990). Indeed, although most of the cardiovascular manifestations associated with hyperthyroidism and hypothyroidism mimic a condition of increased and reduced adrenergic activity, respectively, the sensitivity of the cardiovascular system to adrenergic stimulation does not seem to be substantially altered in these conditions (Hoit *et al.*, 1997; Ojamaa *et al.*, 2000).

Thyroid hormone also exerts an important effect on the vascular system. It acutely reduces peripheral vascular resistance by promoting relaxation in vascular smooth-muscle cells (Klemperer *et al.*, 1995; Ojamaa *et al.*, 1996a; Park *et al.*, 1997). A single study has reported that chronic thyroid hormone excess exerts profound effects on vascular reactivity by improving both endothelium-dependent and -independent mechanisms (Napoli *et al.*, 2001).

III. Overt Hyperthyroidism

Palpitation is one of the most-common symptoms associated with overt hyperthyroidism (Nordyke *et al.*, 1988). Continuous, ambulatory, 24-hour electrocardiogram (ECG) monitoring characteristically demonstrates that heart rate is constantly increased during the day and exaggerated in response to exercise, although its circadian rhythm usually is preserved (von Olshausen *et al.*, 1989; Cacciatori *et al.*, 1996). Analysis of heart rate variability reveals sympatho-vagal

unbalancing with a relative increase in sympathetic tone (Cacciatori *et al.*, 1996). In this respect, although β-adrenergic blockade usually attenuates tachycardia in patients with overt hyperthyroidism, heart rates remain slightly higher, in comparison with euthyroid controls. This supports the notion that thyroid hormone is able to directly affect sinus node firing (Sun *et al.*, 2001).

About 5–10% of overt hyperthyroid patients have atrial fibrillation, which may be the presenting problem (Sawin *et al.*, 1994; Auer *et al.*, 2001). Atrial fibrillation usually reverts to sinus rhythm with achievement of euthyroidism (Nakazawa *et al.*, 1982), the reversion rate decreasing with age and duration of arrhythmia (Nakazawa *et al.*, 1982; Nordyke *et al.*, 1988). Therefore, achievement of the euthyroid state should be the primary treatment strategy of atrial fibrillation associated with overt hyperthyroidism. β-adrenergic blockade may be used effectively to control the ventricular rate. In all instances, electrical or pharmacological cardioversion should be an option only after achievement of euthyroidism. In this context, it remains controversial whether overt hyperthyroid patients with atrial fibrillation should receive anticoagulant therapy. In general, the risk of bleeding with anticoagulant therapy always should be weighed against the risk of systemic embolization (Gilligan *et al.*, 1996) and the decision made on a case-by-case basis. In general, it would be appropriate to administer anticoagulant agents to older patients with known or suspected heart disease or with atrial fibrillation of longer duration (Petersen and Hansen, 1988; Gilligan *et al.*, 1996).

Systolic arterial pressure is almost invariably increased and diastolic arterial pressure decreased in subjects with overt hyperthyroidism, so that pulse pressure is characteristically wider and mean arterial pressure is only marginally decreased (Graettinger *et al.*, 1959; Theilen and Wilson, 1967; DeGroot and Leonard, 1970). These hemodynamic changes are associated with a remarkable increase in cardiac output and a notable reduction in peripheral vascular resistance, thereby resulting in the classic hyperdynamic cardiovascular state (Graettinger *et al.*, 1959; Theilen and Wilson, 1967; DeGroot and Leonard, 1970).

The main determinants of increased at-rest left ventricular (LV) performance in patients with overt hyperthyroidism have not been definitively established (Biondi *et al.*, 2002a). The high cardiac output state results from a remarkably faster heart rate and a slightly augmented stroke volume that, in turn, is associated with normal or marginally enlarged LV end-diastolic size and normal or marginally decreased LV end-systolic size (Biondi *et al.*, 2002a). As a result, LV ejection fraction, an index of overall systolic chamber function, characteristically is increased in overt hyperthyroid subjects (Biondi *et al.*, 2002a). Whether this process is sustained mainly by a true enhancement of myocardial contractility or by the interaction of hemodynamic factors is unclear (Biondi *et al.*, 2002a). Studies by Merillon and colleagues (1981) and by Feldman and coworkers (1986) are emblematic of the controversy surrounding this argument.

Merillon and coworkers (1981) assessed LV function in seven overt thyrotoxic subjects by cardiac catheterization, compared with 11 euthyroid controls atrially paced at a near-identical heart rate. They found no differences between the two groups in such parameters of contractile performance as LV ejection fraction, rate of rise of LV pressure as a proportion of the total pressure, velocity of circumferential fiber shortening, and ratio of LV end-systolic pressure to end-systolic volume. Conversely, it was noted that atrial pacing, but not hyperthyroidism, was accompanied by a marked reduction in both end-diastolic volume and pressure and by a significant increase in systemic vascular resistance and mean aortic pressure. As expected, cardiac performance was not increased in atrially paced subjects. Although atrial pacing and hyperthyroidism are not strictly comparable (acute vs. chronic condition), the authors concluded that there was no realistic increase in the true level of myocardial contractility independent of changes in heart rate and preload in human hyperthyroidism.

Feldman and colleagues (1986) studied LV function in 11 hyperthyroid patients by means of echocardiography and in 11 age-matched normal subjects. They found no differences between the two groups in LV end-diastolic diameter or in end-systolic meridional wall stress. Differently, the rate-corrected mean velocity of circumferential fiber shortening (a measure of LV function claimed to be independent of preload and heart rate) was much higher in hyperthyroid patients. As a result, when LV end-systolic wall stress was related to the rate-corrected velocity of fiber shortening, the values of hyperthyroid patients were above the mean regression line for normal subjects, reflecting the presence of an increased contractile state. The authors, however, did not consider that the normal end-diastolic dimension, despite the augmented heart rate in their patients, corresponded to an effective increase in preload, given the inverse relationship between the two variables. Furthermore, the noninvasive method of assessing myocardial contractility by relating the rate-corrected circumferential fiber-shortening velocity to meridional LV end-systolic wall stress may overestimate myocardial performance in pathophysiological states characterized by simultaneous increases in preload and heart rate.

Based on these remarks, it may be assumed that the notably faster heart rate in hyperthyroid patients masks the actual increase in cardiac preload, leading to an underestimation of the extent to which the Frank-Starling mechanism contributes to improving cardiac performance (Biondi *et al.*, 2002a). Indeed, there is evidence that cardiac preload is increased in overt hyperthyroidism. Some studies have demonstrated clearly that blood volume is enlarged in patients with overt hyperthyroidism (Gibson and Harris, 1939; Anthonisen *et al.*, 1960). Other studies showed that the renin-angiotensin-aldosterone system is activated in hyperthyroid patients (Resnick and Laragh, 1982). In addition, thyroid hormone has been shown to upregulate erythropoietin secretion and, in turn, red blood cell mass, which may also contribute to the increase in total blood volume (Gibson

and Harris, 1939; Graettinger *et al.*, 1959; Klein and Levey, 1984). Moreover, the analysis of LV diastolic function in different investigations has almost invariably revealed an increase in indices of early LV filling and a faster LV relaxation independent of the effect of heart rate (Lewis *et al.*, 1979; Friedman *et al.*, 1982; Mintz *et al.*, 1991; Kahaly *et al.*, 1999). This pattern of diastolic function is consistent with a greater venous return and enhanced ventricular suction, suggesting that the improvement in diastolic function would allow the increased venous return to be accommodated without relevant changes in filling pressure. This interpretation is supported by the observation of comparable values of LV end-diastolic volume and pressure in hyperthyroid patients and normal subjects (Merillon *et al.*, 1981).

It is, therefore, conceivable that the hyperthyroid heart increases its performance through the advantageous modulation of hemodynamic loads, rather than through recourse to its inotropic reserve (Biondi *et al.*, 2002a). In this regard, it is important to underline that the mechanisms that utilize myocardial contractility involve an ever and necessarily greater myocardial metabolic demand. On the contrary, recourse to the hemodynamic loads to improve cardiac performance is an energetically favorable mechanism. Indeed, recourse to the latter mechanism optimizes the cardiac mechanic-energetic utilization in a condition such as hyperthyroidism, in which a clear increase of myocardial energetic consumption is already present (Bengel *et al.*, 2000).

The complicated and delicate interaction between the different factors determining cardiac function in the patient with overt hyperthyroidism may explain, at least in part, two clinical observations. The first, and more frequent, is reduced exercise tolerance (Kahaly *et al.*, 1998,1999); the second – less-frequently encountered than in the past — is development of congestive heart failure (CHF) (Magner *et al.*, 1988). On the one hand, reduced exercise tolerance of hyperthyroid patients may result from their reduced cardiovascular reserve (Kahaly *et al.*, 1998,1999). In fact, the mechanisms used by the cardiovascular system during exercise are almost largely used at rest. On the other hand, CHF may be precipitated by the occurrence of atrial fibrillation. The loss of atrial contribution to ventricular filling and the reduced diastolic time may severely compromise diastolic dynamics, increasing end-diastolic pressure and promoting systemic congestion. Occasionally, CHF may develop as a result of the so-called "rate-related cardiomyopathy" (Magner *et al.*, 1988).

IV. Subclinical Hyperthyroidism

Subclinical hyperthyroidism is characterized by subnormal or suppressed thyrotropin (TSH) serum levels in the presence of circulating thyroid hormones in the normal range for the general population (Biondi *et al.*, 2002c). It may be due to an intrinsic pathology of the thyroid gland (endogenous subclinical

hyperthyroidism) but, more often, is the consequence of suppressive or replacement L-thyroxine (L-T4) therapy (exogenous subclinical hyperthyroidism) (Biondi *et al.*, 2002c). Exogenous subclinical hyperthyroidism is the condition more-frequently seen in clinical practice (Biondi *et al.*, 2002c).

Over past decades, a number of studies have investigated the effects of subclinical hyperthyroidism on the heart, showing that this condition may be associated with important abnormalities of cardiac structure and function (Biondi *et al.*, 2002c). The more-consistent abnormalities found in patients with subclinical hyperthyroidism are increased heart rate and prevalence of supraventricular arrhythmias and enhanced LV 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 latter feature often is associated with slightly enhanced systolic function and almost always with impaired diastolic function due to slowed myocardial relaxation (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 increase in LV mass is due to increased wall thickness without changes of cavity dimension ("concentric remodeling"). It rarely corresponds to an actual LV hypertrophy and is related to the duration of subclinical hyperthyroidism rather than to circulating thyroid hormone levels. The mechanism responsible for the increase in LV mass has not been completely clarified. In general, it is assumed to develop in response to a chronic hemodynamic overload due to the mild hyperkinetic cardiovascular state (Klein, 1988; Fazio *et al.*, 1995). In fact, as happens with classic models of overload-induced cardiac hypertrophy, the increase of LV mass observed in patients with subclinical hyperthyroidism is associated with slowed myocardial relaxation and impaired ventricular filling. It has been suggested that this diastolic dysfunction results from altered intracellular calcium handling due to reduced expression of sarcoplasmic reticulum calcium ATPase and/or increased expression of phospholamban, with the consequent delayed sarcoplasmic reuptake of calcium. However, this view would contrast with the well-known effects of thyroid hormone on such genes (Dillmann, 1990; Kiss *et al.*, 1994). Therefore, it may be hypothesized that, in the long-term, the effects of chronically increased cardiac workload on calcium metabolism would prevail on those promoted by thyroid hormone. Be that as it may, abnormalities of LV morphology and function promptly normalize with achievement of euthyroidism and are effectively attenuated by β-blocking drugs (Biondi *et al.*, 1994,1995,1999b, 2000). This supports the concept that cardiac involvement in subclinical hyperthyroidism is reversible and mostly determined by functional mechanisms.

Importantly, compelling evidence exists that subclinical hyperthyroidism is associated with increased cardiovascular mortality (Parle *et al.*, 2001). Although the mechanism responsible for this association remains obscure, several factors may contribute to this phenomenon (Biondi *et al.*, 2002b). There are indications that patients with subclinical hyperthyroidism, particularly the elderly, have an

increased risk of atrial fibrillation (Sawin *et al.*, 1994; Auer *et al.*, 2001), which may enhance the incidence of thromboembolic events (Petersen and Hansen, 1988; Ladenson, 1993). It has been shown that the increase of LV mass *per se*, even in the absence of a clear LV hypertrophy, and of heart rate are associated with an increased risk of sudden death (Haider *et al.*, 1998; Greenland *et al.*, 1999). Moreover, it is well-recognized that diastolic dysfunction may precede development of more-severe LV dysfunction. Indeed, especially in the elderly, it may precipitate cardiac decompensation and CHF. Therefore, the current opinion is to avoid or correct subclinical hyperthyroidism in all patients affected with benign thyroid disease (Biondi *et al.*, 2002c). On the contrary, when subclinical hyperthyroidism is a therapeutic indication (e.g., in patients with differentiated thyroid cancer), L-T4 should be administered at the lowest dose sufficient to achieve a stable TSH suppression, eventually associated with chronic β-blockade (Biondi *et al.*, 2002c). Contextually, subclinical hyperthyroidism should be suspected in all subjects with a history of atrial fibrillation, especially in the elderly and in those with underlying cardiac disease who complain of worsening of angina pectoris or cardiac decompensation.

V. Overt Hypothyroidism

The cardiovascular effects of thyroid hormone deficiency are opposite to those caused by thyroid hormone excess. However, the clinical presentation of overt hypothyroidism is not obvious and most patients have few symptoms and signs (Klein and Ojamaa, 2000). Bradycardia and systemic hypertension, with narrow pulse pressure and slightly increased mean arterial pressure, and some degree of exercise impairment are the most-common findings in patients with overt hypothyroidism (McAllister *et al.*, 1995; Klein and Ojamaa, 2000).

Many patients with overt hypothyroidism have abnormal standard ECG, including QT interval lengthening and flattening or inversion of the T wave (Fredlund and Olsson, 1983; Klein and Ojamaa, 2000), which reflects the prolonged cardiac action potential (Ojamaa *et al.*, 1999). In addition, overt hypothyroid patients are more prone to ventricular arrhythmias, particularly in the presence of an underlying ischemic heart disease, due to increased electrical dispersion in the myocardium (Fredlund and Olsson, 1983; Klein and Ojamaa, 2000).

The prevalence of systemic hypertension is nearly three-fold higher in patients with overt hyperthyroidism than in euthyroid subjects. In addition, in patients with systemic hypertension, overt hypothyroidism is associated with higher blood pressure (Endo *et al.*, 1979; Saito *et al.*, 1983; Streeten *et al.*, 1988; Klein, 1989; Fletcher and Weetman, 1998; Fommei and Iervasi, 2002). Two factors contribute to systemic hypertension in overt hypothyroidism. The first, and certainly the most-widely recognized, is the remarkable increase in periph-

eral vascular resistance (Klein and Ojamaa, 2000). The second, and more-recently documented, is the increase in arterial stiffness, which likely results from myxedema of the arterial wall (Dernellis and Panaretou, 2002; Obuobie *et al.*, 2002). In general, systemic hypertension associated with overt hypothyroidism is poorly controlled by conventional treatments, whereas it promptly improves with achievement of euthyroidism (Dernellis and Panaretou, 2002). This finding would encourage the routine assessment of thyroid function in all patients with preexisting systemic hypertension that becomes resistant to pharmacological treatment.

The most-consistent cardiac abnormality recognized in patients with overt hypothyroidism is impairment of LV diastolic function, which is characterized by slowed myocardial relaxation and impaired early ventricular filling (Crowley *et al.*, 1977; Wieshammer *et al.*, 1989). LV systolic function usually is only marginally subnormal, as demonstrated by slightly reduced values of ejection fraction and stroke volume (Crowley *et al.*, 1977; Wieshammer *et al.*, 1989). On the one hand, the reduced cardiac preload, in combination with bradycardia and slightly depressed myocardial contractility, accounts for a subnormal cardiac output in overt hypothyroidism (Crowley *et al.*, 1977; Wieshammer *et al.*, 1989). On the other hand, the lower cardiac performance and the abnormalities in peripheral and proximal vascular function may contribute to the poor exercise tolerance in overt hypothyroidism (McAllister *et al.*, 1995).

Occasionally, cardiac function may be further compromised by the development of pericardial effusion, which occurs with severe, long-standing overt hypothyroidism (Ladenson *et al.*, 1992). In addition, overt hypothyroidism may be associated with some increase in LV mass. However, as shown by necropsy and ultrasound investigations, the increase in LV mass does not correspond to myocardial hypertrophy *sensu strictu* but rather to interstitial myxedema (Aber, 1964). By increasing wall stiffness, cardiac myxedema may further compromise LV mechanics, contributing to reduced cardiac output.

In this context, it is important to recall that although overt hypothyroidism is associated with a lower myocardial oxygen demand, myocardial mechanical work efficiency is worse than in euthyroid controls and improves with achievement of euthyroidism (Bengel *et al.*, 2000). The increase in peripheral vascular resistance and arterial stiffness in overt hypothyroidism contributes to increased cardiac afterload, one of the major factors determining myocardial oxygen consumption (Bengel *et al.*, 2000). The disproportionate increase in myocardial oxygen uptake with respect to the level of cardiac performance may, therefore, explain at least in part why overt hypothyroidism may precipitate or worsen angina in patients with suspected or known ischemic heart disease (Keating *et al.*, 1960) and why some of these patients have an improvement in anginal symptoms after thyroid hormone replacement is initiated.

Overt hypothyroidism may be particularly hazardous in the elderly, independent of the presence of underlying cardiovascular disease. Aging is accompanied by the development of cardiac hypertrophy and interstitial fibrosis, which may be responsible *per se* for diastolic dysfunction and reduced cardiovascular performance. Therefore, the onset of overt hypothyroidism in this vulnerable population occasionally may precipitate cardiac decompensation and CHF. In a single study, it was estimated that approximately 30–50% of elderly subjects with heart failure have normal values of ejection fraction (diastolic heart failure) (McDermott *et al.*, 1995). Noteworthy, diastolic heart failure was strongly associated with hypothyroidism and was more prevalent in women (McDermott *et al.*, 1995). Therefore, thyroid function should be routinely assessed in older patients with newly diagnosed or worsening heart failure.

VI. Subclinical Hypothyroidism

Subclinical hypothyroidism (SH), defined by elevated serum TSH level in the presence of normal levels of free thyroid hormones, is common in the adult population, especially among women above 60 years of age (Tunbridge *et al.*, 1977; Canaris *et al.*, 2000). Up to two thirds of patients have serum TSH between 5–10 mU/L and thyroid autoantibodies (Tunbridge *et al.*, 1977; Canaris *et al.*, 2000). Almost half of these individuals may progress to overt thyroid failure (Vanderpump *et al.*, 1995; Huber *et al.*, 2002).

Striking evidence indicates that elevated TSH levels in SH patients do not reflect pituitary compensation to maintain euthyroidism but mild tissue hypothyroidism *sensu strictu* (Andersen *et al.*, 2002). Several changes in metabolic and organ function indexes have been reported in most clinical investigations of patients with persistent SH (Biondi *et al.*, 2002c). Deviation from normality progressively increases with serum TSH level ("dosage effect" phenomenon) (Lekakis *et al.*, 1997; Bindels *et al.*, 1999; Faber *et al.*, 2002).

In general, resting heart rate and blood pressure are normal in SH subjects (Biondi *et al.*, 1999a; Monzani *et al.*, 2001; Di Bello *et al.*, 2002; Vitale *et al.*, 2002). However, significant hypofunctional abnormalities in the parasympathetic nervous system and an increased prevalence of systemic hypertension have been reported in patients with SH (Kahaly, 2000; Luboshitzky *et al.*, 2002).

The most-consistent cardiac abnormality recognized in SH patients is LV diastolic dysfunction, characterized by slowed myocardial relaxation and impaired early ventricular filling, both at rest and with exercise (Biondi *et al.*, 1999a; Monzani *et al.*, 2001; Di Bello *et al.*, 2002; Vitale *et al.*, 2002; Brenta *et al.*, 2003). Often, this is associated with a variable impairment in LV systolic function at rest (Biondi *et al.*, 1999a; Monzani *et al.*, 2001; Di Bello *et al.*, 2002; Vitale *et al.*, 2002), which becomes more consistent on exercise (Foldes *et al.*, 1987; Kahaly, 2000; Brenta *et al.*, 2003). In a comprehensive study of exercise

capacity, it was reported that SH is associated with impairment of several exercise-related cardiopulmonary responses, resulting in some degree of exercise impairment (Kahaly, 2000).

Recently, a strong association between SH and atherosclerotic cardiovascular disease, independent of the traditional risk factors (i.e., hypercholesterolemia, hypertension, smoking, diabetes mellitus), was noted in a large cross-sectional survey of postmenopausal women (the Rotterdam Study) (Hak *et al.*, 2000). Although the mechanism responsible for this association remains to be clarified, compelling evidence indicates that SH is associated with an atherogenic lipid profile, characterized by increased circulating levels of total and low-density cholesterol and increased levels of oxidized low-density lipoproteins (Duntas, 2002; Duntas *et al.*, 2002). It has been reported that SH may affect the hemostatic profile, thereby promoting a hypercoagulable state (Müller *et al.*, 2001). Moreover, a reduced endothelium-dependent, flow-mediated vasodilation, which is an early marker of atherosclerosis, has been reported in patients with SH (Lekakis *et al.*, 1997).

Importantly, when SH patients are treated with L-T4, most metabolic and cardiovascular abnormalities improve or even normalize (Danese *et al.*, 2000; Biondi *et al.*, 2002c). However, whether patients with SH should be treated remains the subject of disagreement (Chu and Crapo, 2001; McDermott and Ridgway, 2001).

VII. Thyroid Function in Cardiovascular Disorders

The relationship between thyroid status and the cardiovascular system is not unidirectional. A body of data indicates that acute and chronic cardiovascular disorders may alter the metabolism of thyroid hormone.

Within 4 hours after acute uncomplicated myocardial infarction, circulating T3 and T4 levels are reduced by about 20% and 40%, respectively (Franklyn *et al.*, 1984). In patients with chronic heart failure, serum thyroid hormone concentration decreases and reverse-T3 increases, the magnitude of changes paralleling the degree of functional impairment as assessed by the New York Heart Association classification (Hamilton *et al.*, 1990). In patients undergoing cardiopulmonary or coronary-aortic bypass surgery, circulating T3 levels fall significantly in the postoperative period (Holland *et al.*, 1991; Klemperer *et al.*, 1995; Bettendorf *et al.*, 1997).

In this regard, several lines of evidence suggest that the altered thyroid status in patients with cardiovascular disorders could modify cardiac gene expression and contribute to impaired cardiac function (Klein and Ojamaa, 1998). In animals, a low serum concentration of T3 induced by caloric restriction was associated with impaired cardiac contractility and altered gene expression similar to that seen in experimental hypothyroidism, which normalized with replacement

doses of T3 (Katzeff *et al.*, 1997). Decreased expression of thyroid hormone nuclear receptor α-1 associated with increased expression of the thyroid hormone nuclear receptor α-2, typical of tissue hypothyroidism, recently was reported in myocardial biopsy from patients with chronic heart failure (Kinugawa *et al.*, 2001). Of note, this abnormal pattern of thyroid hormone receptor expression was correlated with the reduced myocardial expression of the α-isoform of myosin heavy chain and the increased expression of the β-isoform of myosin heavy chain and of the atrial natriuretic peptide, thereby implicating tissue thyroid status in the development of the failing heart phenotype (Kinugawa *et al.*, 2001). In 23 patients with advanced chronic heart failure, a single intravenous dose of T3 elicited a significant hemodynamic improvement by reducing peripheral vascular resistance and increasing cardiac output (Hamilton *et al.*, 1998). Treatment with low-dose L-T4 daily for 12 weeks greatly benefited 20 patients with chronic heart failure by reducing peripheral vascular resistance, increasing cardiac output, and improving exercise performance (Moruzzi *et al.*, 1996). Moreover, in patients undergoing cardiopulmonary or coronary artery bypass surgery, intravenous treatment with T3 immediately before and/or after surgery significantly improved postoperative cardiac function and reduced somewhat the extent of surgical mortality (Klemperer *et al.*, 1995; Cimochowski *et al.*, 1997; Mullis-Janson *et al.*, 1999; Bettendorf *et al.*, 2000). In no instance did thyroid hormone treatment deteriorate cardiac function or induce myocardial ischemia rhythm disturbances or other untoward effects (Klemperer *et al.*, 1995; Moruzzi *et al.*, 1996; Cimochowski *et al.*, 1997; Hamilton *et al.*, 1998; Mullis-Janson *et al.*, 1999; Bettendorf *et al.*, 2000).

In line with these preliminary observations, studies with experimental models of LV dysfunction and preliminary clinical investigation of patients with chronic heart failure reported that the thyroid hormone analog 3,5-diiodothyropropionic acid, whose biological activity profile is similar to that of thyroid hormone except for effects on heart rate, elicited relevant hemodynamic improvements by reducing systemic vascular resistance and improving both systolic and diastolic LV function. This was accompanied by an increase in cardiac output and improved lipid profile (Morkin *et al.*, 2002).

VIII. Conclusion

Thyroid dysfunction causes remarkable cardiovascular derangements. Because signs and symptoms referable to the cardiovascular system may be the only manifestations of overt thyroid dysfunction and because persistent subclinical thyroid dysfunction may notably increase the cardiovascular risk, thyroid status should be systematically investigated in all patients with newly diagnosed or worsening cardiovascular disease, especially the elderly. In addition, patients with acute or chronic cardiovascular disorders have abnormalities in peripheral

thyroid hormone metabolism that may alter cardiac function. The finding that administration of thyroid hormone or its analog 3,5-diiodothyropropionic acid may greatly benefit these patients should foster further investigation in this area.

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