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Thyroid Hormone Action in the Heart

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The heart is a major target organ for thyroid hormone action, and marked changes occur in cardiac function in patients with hypo- or hyperthyroidism. T_3-induced changes in cardiac function can result from direct or indirect T_3 effects. Direct effects result from T_3 action in the heart itself and are mediated by nuclear or extranuclear mechanisms. Extranuclear T_3 effects, which occur independent of nuclear T_3 receptor binding and increases in protein synthesis, influence primarily the transport of amino acids, sugars, and calcium across the cell membrane. Nuclear T_3 effects are mediated by the binding of T_3 to specific nuclear receptor proteins, which results in increased transcription of T_3-responsive cardiac genes. The T_3 receptor is a member of the ligand-activated transcription factor family and is encoded by cellular erythroblastosis A (c-erb A) genes. T_3 also leads to an increase in the speed of diastolic relaxation, which is caused by the more efficient pumping of the calcium ATPase of the sarcoplasmic reticulum. This T_3 effect results from T_3-induced increases in the level of the mRNA coding for the sarcoplasmic reticulum calcium ATPase protein, leading to an increased number of calcium ATPase pump units in the sarcoplasmic reticulum. (*Endocrine Reviews* 26: 704–728, 2005)

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Abbreviations: AF, Atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HCN, hyperpolarization cyclic nucleotide; KO, knock-out; LDL, low-density lipoprotein; LV, left ventricle; MHC, myosin heavy chain; NHE, Na/H exchanger; PEP, preejection period; RXR, retinoic X receptor; SERCa, calcium ATPase of the sarcoplasmic reticulum; SMR, standardized mortality ratio; TH, thyroid hormone(s); TR, thyroid hormone receptor; TRE, T_3 response element; TSH-R, TSH receptor.

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I. Introduction

THE CLOSE LINK between the thyroid gland and the heart was clear in the earliest descriptions of hyperthyroidism. Influences of increased thyroid hormone (TH) secretion on cardiovascular function were noticed more than 200 yr ago. In 1785, a British physician, C. Parry, noted for the first time an association between the swelling of the thyroid area and heart failure (1). Parry described eight cases, all women, with a thyroid enlargement, a rapid heartbeat, and palpitations, and four were judged to have cardiac enlargement. From his descriptions of the pulses, it is likely that his first patient had atrial fibrillation (AF). In his paper, published in 1825, he stated: "There is one malady which I have in five cases seen coincident with what appeared to be an enlargement of the heart. The malady to which I elude is enlargement of the thyroid gland." An Irish physician, R. Graves described 50 yr later: "four cases of violent and long continued palpitation in females with thyrotoxicosis" (2). On the European continent, the cardiac aspects of hyperthyroidism were also noted by C. von Basedow (3), a practitioner in Merseburg, Germany, who in 1840 reported three cases with goiter, palpitations, and exophthalmos. The cardiovascular manifestations of myxedema remained essentially unrecognized until 1918, when H. Zondek of Munich (4) described

what he termed "Das Myxödemherz," noting all of the classical clinical and electrocardiography features of far advanced myxedema except for pericardial effusions. He also noted the reversibility of these changes upon treatment with thyroid extract. The decades following these original descriptions were characterized predominantly by clinical observations related to cardiovascular effects of excessive TH: arrhythmias, changes in cardiac contractility, and peripheral vasodilatation (5).

II. Cardiovascular Mechanisms of THs

A significant effect of THs on the heart results from an interaction with specific nuclear receptors in cardiac myocytes. However, rapid TH effects on ion transport functions have been elicited in isolated cardiac myocytes and may be independent of protein synthesis. Under such circumstances, THs do not appear to function by first binding to nuclear receptors. However, such proposed extranuclear effects are less well characterized than are the interactions of THs with nuclear receptors. Overall, changes in TH status influence cardiac action by three different routes: 1) the biologically relevant TH, T_3, exerts a direct effect on cardiac myocytes by binding to nuclear T_3 receptors influencing cardiac gene expression; 2) T_3 may influence the sensitivity of the sympathetic system; and 3) T_3 leads to hemodynamic alterations in the periphery that result in increased cardiac filling and modification of cardiac contraction (6–16). In contrast to humans (17), rodents do not express the type 2 iodothyronine deiodinase in their myocardium, and conversion of T_4 to T_3 does not occur to any measurable degree in rodent cardiac myocytes (18, 19).

A. TH receptor (TR) isoforms

In 1986, it was demonstrated that the cellular homolog of the cerb-A protooncogene binds T_3 with high affinity and limited capacity and has binding characteristics identical to the nuclear T_3 receptor (20, 21). Two separate genes, TRα and TRβ, code for several mRNAs, each representing a splice variant (22). The splice variants of the TRα gene lead to the T_3 binding isoform TRα1 and a 3′-splice variant TRα2, which does not bind T_3. This isoform seems to have a modest inhibitory effect on nuclear T_3 action. Recently, $\Delta\alpha$1 and $\Delta\alpha$2 isoforms have been identified that are transcribed from a novel promoter in intron 7 of the TRα gene (23). These shorter variants lack the DNA binding domain and act as dominant-negative antagonists (24). The TRβ gene exhibits 5′-splice variants leading to the widely distributed TRβ1 mRNA and the TRβ2 mRNA, which is concentrated primarily in the pituitary. An additional isoform, TRβ3, was more recently identified and is transcribed from a third TRβ promoter (25). Prior findings indicate that 40% of T_3 binding of heart-binding capacity is due to the TRα1 receptor and a similar percent is due to TRβ1. In addition, 20% of total T_3 binding capacity is provided by TRβ2 receptor in the rat heart (26). More recent findings indicate that in mouse hearts, TRα1 presents 70% of total cardiac TR mRNA and TRβ1 presents 30% (27, 28). Results on the protein levels for TRα1 and TRβ1 are currently not available aside from the studies mentioned above (26). It should be noted that more recent studies have not found significant amounts of TRβ2 mRNA in the mouse heart (27). Studies in TRα knock-out (KO) mice show that TRα1 action is predominant in the heart (27, 28).

B. TH action mediated by nuclear receptors

Direct effects of T_3 on cardiac function are mediated by binding of T_3 to its nuclear receptor sites (22). T_3 receptors can bind to their response elements as monomers, homodimers, or heterodimers composed of a T_3 nuclear receptor and another receptor from the steroid hormone receptor family (29, 30). The retinoic X receptor (RXR) is one of the preferred heterodimerization partners for the T_3 receptor. In general, the T_3R-RXR heterodimers bind with higher affinity to T_3 response elements (TREs) and have increased transactivation activity stimulating the transcription of T_3-responsive genes. Binding of the T_3-occupied receptor to TREs leads to increased transcription of many T_3-responsive cardiac genes. This process probably occurs through stabilization of the transcriptional preinitiation complex (29–32). Occupancy of receptors by T_3 in combination with recruited coactivators leads to optimal transcriptional activation. In the absence of T_3, the receptors repress genes that are positively regulated by THs. The sequence of events leading to nuclear T_3 effects can be briefly described in the following manner. T_3 enters the cell, and part of this entry may be mediated through a stereo-specific transport mechanism. T_3 then crosses the nuclear membrane to enter the nucleus. A nuclear TRα complex binds to specific TRE stretches of 10–20 nucleotides, which are localized in the vicinity of the transcriptional start site of T_3-responsive genes. Binding of T_3 to TR and/or to TREs leads to the formation of an active transcription complex to which coactivators are recruited. The TR-T_3 coactivator interaction results in increased histone acetylation and opening up of the chromatin structure and allows for enhanced transcriptions (22, 29, 30). Enhanced transcription of T_3-responsive genes ensues; increased amounts of mRNA are produced and translated into specific proteins. T_3-induced increases in specific mRNA can be mediated by posttranscriptional alterations (10). Further modification of T_3 receptor action is provided by interactions of the TR with other receptors such as the RXR and cell type-specific factors. In addition, posttranslational modifications of TRs, such as phosphorylation, occur (33).

C. TH-responsive genes

To link T_3-induced changes in the expression of specific genes to contractile events, the cardiac contraction cycle will be discussed. The cardiac cycle is divided into systolic contraction and diastolic relaxation. Processes related to contraction are termed "inotropic mechanisms," and mechanisms related to relaxation are termed "lusitropic effects." T_3 markedly shortens diastolic relaxation, *i.e.*, the hyperthyroid heart relaxes with a higher speed (lusitropic activity), whereas diastole is prolonged in hypothyroid states in all mammalian species (34). The speed with which the free calcium concentration is lowered in the cytosol, making less calcium available to troponin C of the thin filament of myofibrils, is one of the crucial events leading to

diastolic relaxation. Several calcium pumps and ion exchangers contribute to the lowering of calcium, but the most important contribution is made by the calcium pump localized in the sarcoplasmic reticulum (35). The sarcoplasmic reticulum is a vesicular structure surrounding the myofibrils. The gene coding for the calcium pump of the sarcoplasmic reticulum is markedly T_3 responsive. Three TREs have been identified in the regulatory region of this gene (36–38), and T_3 markedly increases expression of the sarcoplasmic reticulum Ca^{++}ATPase (SERCa2) gene under *in vivo* conditions. T_3-induced increases in transcription can be demonstrated in cultured cardiac myocytes, thus indicating that this is a direct T_3 effect. Of interest, α1-adrenergic stimulation inhibits 3,5,3′-T_3-induced expression of the rat heart SERCa2 gene (39). Release of calcium and its reuptake into the sarcoplasmic reticulum are critical determinants of systolic contractile function and diastolic relaxation (40). SERCa2 activity is influenced by phospholamban and its phosphorylation, which is influenced by the thyroid status (41–44).

The mRNA coding for the ryanodine channel, the calcium channel of the sarcoplasmic reticulum, is also markedly upregulated by THs (45). The increased number of ryanodine channels results in T_3-induced increases of calcium release from the sarcoplasmic reticulum during systole and probably accounts, in large part, for the increased systolic contractile activity of the hyperthyroid heart. Several plasmamembrane ion transporters, such as Na^+/K^+-ATPase, Na^+/Ca^{++} exchanger, and voltage-gated potassium channels, including Kv1.5, Kv4.2, and Kv4.3, are also regulated at both the transcriptional and posttranscriptional levels by THs, thus coordinating the electrochemical and mechanical responses of the myocardium (46, 47). In contrast, calsequestrin, a calcium-binding protein of the sarcoplasmic reticulum, is not modulated by alterations in thyroid status. In the sarcolemma cell membrane of the myocytes, a calcium pump removes calcium from the cytosol. As indicated previously, this calcium pump appears to be influenced by THs in isolated membrane fractions, a finding suggesting an extranuclear effect (48). The Na^+/K^+ATPase is also localized in the sarcolemma and indirectly influences calcium concentration. It is also influenced by the thyroid status. Up-regulation of the α1-, α2-, and β-subunits occurs in the transition from the hypo- to the euthyroid state. The Na^+/K^+ATPase is only one of several ATP-consuming ion pumps that contribute to the increased oxygen consumption of the hyperthyroid heart (Tables 1 and 2).

TABLE 1. TH regulation of genes coding for cardiac proteins

Positive regulation
Sarcoplasmic reticulum calcium adenosine triphosphatase
Myosin heavy chain α
β1-Adrenergic receptors
Guanine-nucleotide-regulatory proteins
Sodium/potassium adenosine triphosphatase
Voltage-gated potassium channels
Negative regulation
T_3 nuclear receptor α1
Myosin heavy chain β
Phospholamban
Sodium/calcium exchanger
Adenylyl cyclase types V and VI

Typical examples of T_3-induced alterations in specific cardiac contractile proteins are the changes in myosin isoenzymes and myosin heavy chain (MHC) isoforms in rat and rabbit hearts (49, 50). The myosin holoenzyme consists of two MHCs and four light chains. Myosin V1, which predominates in the normal heart, consists of two MHCα whereas V3 contains two MHCβ, and V2 is a heterodimer of MHCα and -β. Myosin ATPase activity of V1 is markedly higher than that of V3. Changes in myosin isoenzyme predominance in animal hearts are regulated by T_3-induced alterations in the expression of the gene coding for MHCα and -β. T_3 administration stimulates the expression of the MHCα gene but decreases the expression of the MHCβ gene. In the hypothyroid heart, V3 predominates, and myosin with low ATPase activity participates in the contractile process (49). This leads to the decreased velocity of contraction of the hypothyroid papillary muscle. In contrast, in hyperthyroid rat hearts, myosin is exclusively composed of V1, which leads to a fast turnover of the globular head of myosin moving along the thin filament and to accelerated contraction. Binding of the occupied T_3 receptor to these TREs in the MHCα gene promoter leads to a marked increase in MHCα transcription (49–51). In the promoter of rabbit MHCβ, a negatively acting TRE has been described (49). The marked T_3-induced changes in myosin isoenzyme predominance occur primarily in small animals. In human hearts, MHCβ presents more than 95% of the myosin isoenzyme (52), and it is not changed significantly by the thyroid status. However, in a reported hypothyroid patient with severe biventricular failure, in which the left ventricular (LV) ejection fraction increased from 14–44% after 9 months of T_4 therapy, mRNA was extracted from pre- and posttreatment endomyocardial biopsy specimens, and mRNA species representing T_3-responsive myocardial genes were amplified by PCR. The steady-state concentration of MHC increased 11-fold, with a minimal reduction in the β-MHC level, suggesting that T_3-regulated expression of the MHC isoenzyme genes may play a role in T_3 modulation of human myocardial contractility (53).

TH also leads to a marked increase in cardiac actin, which is part of the thin filament. With marked and persistent hyperthyroidism there is also an increase in the formation of skeletal actin. The regulatory cardiac protein troponin I that is part of the thin filament is also influenced by the thyroid status. The TH especially influences the level of the cardiac troponin I isoform in postnatal and young adult rats by increasing the expression of the gene coding for this protein (54).

Cardiac myocytes represent one third of the cells of the heart but, due to their large size, they contain two thirds of cardiac proteins. In contrast, cardiac fibroblasts represent two thirds of all cardiac cells but are much smaller (55). Fibroblasts contain only one tenth the number of TRs per cell in comparison with cardiac myocytes. The vascular system of the myocardium contributes a small number of cardiac cells, including endothelial and vascular smooth muscle cells (55). Hyperthyroidism increases total protein synthesis in cardiac myocytes, resulting in increased heart weight and a mild degree of cardiac hypertrophy, which contributes to the increased contractile state. T_3-induced hypertrophy is com-

TABLE 2. TH effects in the heart

Gene	Transcription	TRE	mRNA	Protein	Activity
Myocytes—myofibrils					
MHC α	↑	Yes	↑ ↑ ↑	↑ ↑ ↑	Speed contraction ↑
MHC β	↓	Yes	↓ ↓ ↓	↓ ↓ ↓	Speed contraction ↓
C-actin	N/D	N/D	↑ ↑ ↑	N/D	Thin filament contractile protein
S-actin	N/D	N/D	↑ ↑ ↑	N/D	Thin filament contractile protein
Troponin I	N/D	N/D	↑ ↑ ↑	N/D	Thin filament regulatory protein
Myocytes—sarcoplasmic reticulum					
SERCA 2	↑	Yes	↑ ↑ ↑	↑ ↑ ↑	Ca sequestration ↑
Phospholamban	N/D	N/D	↓ T3/↓ Tx	N/D	SERCA 2 inhibition
Ryanodine channel	N/D	N/D	↑ ↑ ↑	N/D	Ca Efflux ↑
Myocytes—sarcolemma					
NaK ATPase					
α1			↑ Tx→E	↑ Tx→E	Na Efflux ↑
α2			↑ Tx→E	↑ Tx→E	
β			↑ Tx→E	↑ Tx→E	
βi Receptor	↑	N/D	↑ ↑	↑ ↑	Adrenergic ↑
Gi α	N/D	N/D	↓ ↓	↓ ↓	Adrenergic ↓
Gi β	N/D	N/D	↓ ↓	↓ ↓	Adrenergic ↓
Gs	N/D	N/D	N/D	↑	Adrenergic ↑

↑, An increase of parameter after TH administration; ↓, a decrease in the hypothyroid state; N/D, not determined; E, extranuclear effect.

pletely reversible with restoration of the euthyroid status. Total and specific mRNA levels and protein synthesis increase by about 30%. T_3 effects generated in the vascular system influence primarily total cardiac protein synthesis, as demonstrated in hearts that are not hemodynamically loaded (56). In contrast, T_3 effects on the expression of specific genes, such as SERCa2 or MHCα, result from direct effects of T_3 in cardiac myocytes. Addition of T_3 to cardiac myocytes in cell culture results in an increase in protein synthesis (57). In contrast, cardiac fibroblasts do not participate in this hypertrophy process, and collagen levels decrease in the hyperthyroid heart (58). The influence of T_3 on the expression of specific cardiac genes that participate in the cardiac contractile process is summarized in Table 2.

Overall, T_3 markedly stimulates enzymes involved in calcium and ion flux. These enzymes significantly contribute to ATP breakdown in the cell and to the stimulatory effect of T_3 on oxygen consumption. Studies in which the use of the chemical energy stored in ATP was measured in heart muscles from animals of different thyroid status have indicated that, in hyperthyroid hearts, a larger fraction goes to heat production, whereas in euthyroid animals more is spent for useful contractile energy. This inefficient use of chemical energy may explain the well-established finding that hyperthyroidism of long duration and great severity leads, in the end, to cardiac failure. Finally, THs modify the secretory activity of the heart. Atrial natriuretic factor is produced in the normal heart in the myocytes of the atrium, and T_3 increases mRNA and protein levels of the atrial natriuretic factor (57, 59). THs also influence the metabolic activity of the heart and T_3-induced increases in the mRNA level for cardiac malic enzyme.

D. Contractile and electrical activity of the heart

The precise molecular events that underlie the recognized manifestations of the influence of the TH on the electrical activity of the heart have been incompletely explored. T_3-induced increases in the recruitment of slower inactivating sodium channels have been described (60). Thyroid status also influences potassium channels. The activity of a specific potassium channel, the Ito channel, which participates in early repolarization, is reduced in cardiac myocytes from hypothyroid rats and is normalized when these animals are treated with T_3 (61). Hyperthyroidism also modifies specific potassium current in rabbit myocytes (62). The influence of T_3 on another potassium channel accelerates the decline in the action potential. The effects of T_3 on calcium channels have also been described (63, 64). Many T_3-induced changes in channel behavior may occur as a result of changes in channel subunit expression and subunit composition. Heart rate effects are mediated by T_3-based increases in the pacemaker ion current I_f in the sinoatrial node. The proteins constituting the I_f channel are hyperpolarization cyclic nucleotide (HCN) gene products with HCN1, HCN2, and HCN4 expressed in the sinoatrial node and up-regulated T_3. The L-type Ca channel ID, which also serves important pacemaker functions, is also increased by T_3.

E. Extranuclear effects of THs in the heart

Extranuclear or nongenomic actions of THs do not require formation of a nuclear complex of the hormone and occur very rapidly. In contrast to T_3 effects mediated by nuclear receptors, which take at least 0.5–2.0 h to demonstrate, T_3-induced changes in ion flux can be demonstrated within several minutes (65, 66). For example, T_3 addition leads to a rapid recruitment (within 4 min) of slowly inactivating sodium channels in cardiac myocytes. A direct, nuclear receptor-independent effect of THs on the Ca^{++}ATPase of the sarcolemma has been described that occurs in reconstituted membranes and therefore represents an extranuclear effect of THs (67). T_3 also stimulates the Ca^{++}ATPase activity as well as the calcium movement across the membrane, which are due to changes in calcium channels (68, 69). Furthermore, marked T_3-induced increase in the activity of the cardiac Na^+/K^+ATPase has been demonstrated (70). This enzyme is located in the cardiac cell membrane and extrudes Na^+ from

the anterior of the cell in exchange for extracellular K^+. In contrast, limited evidence has accumulated for T_3 influence on the transport of sugars and amino acids across plasma membranes (71). THs are highly lipophilic compounds, and it is conceivable that THs are concentrated in the phospholipid bilayer of the plasma membrane of cardiac myocytes. T_3 concentrated in the plasma membrane may influence specific ion channels.

Extranuclear and TR-dependent (nuclear) actions of THs may interface. For example, T_4 nongenomically causes serine phosphorylation of TR, and THs act via TR on the gene for SERCa2 and also lead to nongenomic effects on the activity of the protein (72–74). Several nongenomic actions of THs on the heart are potentially important. There are actions in the euthyroid state on homeostatic functions (ion pumps, channels) at the plasma membrane (sarcolemma). These include stimulation of the membrane Na/H antiport (75, 76) or exchanger (NHE) and calcium pump (Ca^{++}-ATPase). Because circulating levels of THs are relatively constant, actions of the hormone on NHE and Ca^{++}-ATPase would contribute to basal activity or set points of these transporters. The actions on channels may determine set points of myocardial excitability and duration of the action potential (77). Among the functions affected are sodium current and inward rectifier K channel (78). Second, nongenomic actions may affect contractility (dP/dT). The test of significance of these effects that have occurred in the animal heart or in cells is whether, in the hypothyroid state in man, these apparently homeostatic actions are disordered. Mechanisms of these actions are only partially understood. There are two other settings in which nongenomic actions of T_3 on the heart are potentially important. One is the euthyroid sick state in which circulating levels of T_3 are reduced. Nongenomic effects of THs on NHE, TRE, inward rectifier K channel, and action potential are mediated primarily by T_3, whereas effects on the calcium pump and on serine phosphorylation are T_4 dependent. The second is ischemia/hypoxia. Here, the issue is whether hormone actions are modulated by hypoxia. Recently, THs have been shown in physiological or near-physiological concentrations to have apparently cardioprotective actions in the ischemic animal heart and in rescue of myocardial function after human cardiopulmonary bypass surgery. Particularly relevant is the NHE. Inhibition, rather than stimulation, of the latter in ischemia has recently been shown to preserve myocardial function (79). Importance of these hormonal actions requires their evaluation in myocardium in models of the euthyroid sick syndrome and of heart ischemia. Up to now, demonstration of extranuclear T_3 effects has occurred only in cell culture systems. Cell surface receptors for THs have been described, but these binding sites are of low affinity and high capacity and may function in facilitating T_3 transport into cells (80).

F. Animal models of TH action in the heart

1. TR KO mice and cardiovascular phenotype. Interesting cardiovascular phenotypes have been observed in mouse lines in which either TRα or TRβ, or both, have been deleted (81–85). The most striking cardiac phenotype in such null mutants occurs in mice with deletions of the TRα leading to significant bradycardia. A TRα splice mutant mouse was engineered in which only the TRα2 isoform, which does not bind T_3, is expressed and the T_3-binding α1 is deleted by altering the splice possibility in the ninth exon of the TRα gene (81). Mice with deletions of exon 2 of the TRα were also generated (82, 83). TR$\alpha^{-/-}$ mice have a decreased body size, hypothermia, a limited life span, and do not reproduce. A second line of TRα KO mice was constructed in which exons 5 and 6 of the TRα gene are deleted, TR$\alpha^{0/0}$. In TR$\alpha^{-/-}$ and TR$\alpha^{0/0}$ mice, bradycardia occurs with decreases in level of the recently identified cyclic nucleotide-gated ion channel genes HCN4 and HCN2 mRNA in the cardiac ventricle and the atrium. Both of these mRNAs were T_3 responsive in the ventricle; however, in the atrium only HCN2 appears to be T_3 responsive (27). Individual TR isoform KO mice were also used to study the effects of TRα and -β in the heart (27). The findings indicate that K^+ channel genes that code for K^+ channels involved in action potential repolarization, such as KV 4.2 and minK, are TRα targets. Both are markedly regulated by thyroid status. HCN2 and -4 are targets of TRα and are unchanged in a euthyroid TRβ KO. However, these transcripts respond markedly to altered T_3 signaling concomitant with bradycardia in TRα KO and hypothyroid animals, as well as tachycardia in hyperthyroid TRβ KO mice. SERCa2 and myosins are T_3 regulated and were also targets of TRα, and the papillary muscles of α-KO animals showed a slowed rate of force development. Because of the absence of significant cardiac effects in euthyroid TRβ KO mice, mRNA levels for both TRα and TRβ in the heart were determined. TRβ was present at a 1:3 ratio to TRα1 (27). Thus, the cardiac phenotype regulated by T_3 is primarily mediated by the more predominant TRα in the heart (Table 3).

In TRα KO mice, the mRNA for the rectifier K^+ channel Kv 4.2 that codes for the ITO channel, which is activated during the first and second phase of the action potential, is markedly decreased. In addition to the marked changes in heart rate and corresponding alterations in ion channel genes, the contractile phenotype was also markedly impaired in TRα KO mice. Papillary muscle obtained from these mice showed a diminished contractile function. In line with the decreased contractile phenotype, the mRNAs coding for proteins involved in cardiac contraction such as MHC-α or SERCa2

TABLE 3. TR knockout/in mice and cardiovascular phenotype

	TR$\alpha^{-/-}$	TR$\alpha^{0/0}$	TRα1$^{-/-}$	TR$\beta^{-/-}$	Hypothyroidism
TSH	↓	→	↓	↑	↑
T_3	↓	→	→	↑	↓
Heart rate	↓	↓	↓	→	↓
Ion channel genes HCN 2/4 mRNA	↓	↓	↓	→	↓
Contractile function	↓	↓	↓	→	↓
Serca mRNA	↓	↓	↓	→	↓
MHCα mRNA	↓	↓	↓	→	↓
MHCβ mRNA	↑	↑	↑	→	↑
Body temperature	↓	↓	↓	→	↓

TR$\alpha^{-/-}$ mice have deletion of exon 2; TR$\alpha^{0/0}$ have deletions of exons 5, 6, and 7; TR$\beta^{-/-}$ have deletions of exons 4 and 5; TRα1$^{-/-}$ mice have a fusion of part of exon 9 and exon 10 and transcribe only TRα2 that does not bind T_3. [Derived from Refs. 27, 73–75, and 80.]

were markedly diminished, and the mRNA coding for MHC-β was markedly increased. In contrast to the marked electrical and contractile alterations observed in TRα KO mice, no significant electrophysiological or contractile changes were observed in the hearts of TRβ KO mice. These mice have elevated serum TH levels because the TRβ_2 protein that normally suppresses TSH expression in the pituitary is absent. When TRβ KO mice are made euthyroid, electrical and contractile activity similar to that observed in wild-type mice is found. Comparison of the cardiac phenotype between TRα and TRβ KO mice clearly indicates that TRα has predominant contractile and electrophysiological function in the heart. Despite these results, it appears that the TRβ does contribute to cardiac action (86). For example, in TRα KO mice in which TRβ is the only remaining functional TR, T_3 administration can increase the heart rate from a decreased level (87). T_3 administration does not normalize heart rate, but the significant T_3-induced increase in heart rate in the TRα KO must be mediated by a TRβ effect in the myocytes of the sinus node. Mice with a T_3 receptor mutant leading to TH resistance have marked bradycardia (88). These findings would indicate that although TRα is markedly more predominant in the heart and probably in the sinus node, TRβ is also expressed in the cells of the pacemaker center in the sinus node. Mice in which both TRα and TRβ are deleted are viable, have high T_3 levels, and exhibit bradycardia and hypothermia and therefore resemble a hypothyroid phenotype (82).

2. Models of resistance to TH. Tachycardia may be seen in patients with resistance to THs, which is believed to reflect the effect of elevated TH concentrations on the heart (85) (Fig. 1). The heart is relatively less resistant than other organs, possibly because TRα is more predominant than TRβ. The liver and pituitary express predominantly TRβ receptors and show more T_3 resistance. Therefore, mutations in TRβ are likely to be associated with pituitary and liver resistance, whereas the tachycardia may represent retention of cardiac sensitivity to TH acting via a normal TRα receptor. Indeed,

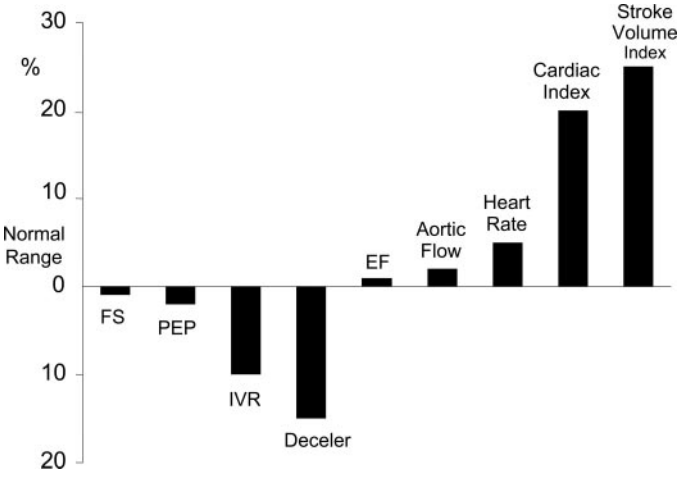

FIG. 1. Changes of various cardiovascular parameters (evaluated by noninvasive two-dimensional and Doppler echocardiography) in 52 patients with resistance to thyroid hormone. EF, Ejection fraction of the LV; FS, fractional shortening of the LV; IVR, isovolumic relaxation time; Decel, diastolic deceleration time. [Derived from Ref. 85.]

TRβ-deficient mice have a normal TH-dependent increase in heart rate, whereas mice deficient in TRα1 manifest bradycardia (87). Less is known about the impact of mutant TR expression on cardiac function. THs alter myocardial contractility, in part, by altering the expression of the MHC genes. To investigate the direct cardiac effect of mutant TR expression on cardiac function, a transgenic mouse, which expresses the mutant Δ337T (β1 isoform), was generated exclusively in the heart (89). Transgenic mice had normal TH serum levels. In mice with mutant TR expression, there was marked induction of the β-MHC mRNA and reduction in α-MHC expression, which are changes similar to those seen in hypothyroid hearts (49). Treatment of these mice with THs was not associated with either down-regulation of β-MHC expression or up-regulation of α-MHC expression indicating resistance to THs. Contractile function, measured *in vivo* and in isolated perfused heart preparation, showed cardiac abnormalities similar to those present in hypothyroid animals, such as prolonged QRS in the electrocardiogram (ECG), reduced LV-developed pressure, and reduced dp/dt, which is a measure of the rate of change of contraction and relaxation indicating LV dysfunction. These data indicate that, in the heart, a strong dominant-negative TRβ isoform like Δ337T can efficiently oppose and overwhelm the effects of the normally predominant TRα1. These findings also indicate that most cardiac myocytes express both TRα1 and TRβ1.

Electrophysiological and contractile changes of the heart in transgenic mice that overexpress the Δ337T mutants have also been reported (90). The expression of ion channels in the heart of mice carrying the human resistance to TH mutant receptor was examined and was compared with TR isoform KO as well as hypo- and hyperthyroid mice. The most significant changes occurred in the voltage-gated K^+ channels Kv1.5, Kv4.2, and HAC1. Little or no change was seen in Kv4.3 and Kv1.4. This parallels the changes in the T_3Rβ KO hearts but was different from the changes observed in T_3Rα KO, hypo- and hyperthyroid hearts. These results provide a molecular explanation for the hypothyroid contractile phenotype but normal heart rate of the transgenic mice carrying the Δ337T mutant, which did not show a lower expression of the peacemaker channel HCN2, observed in hypothyroid animals.

More recently, mice were described in which the endogenous TRβ promoter drives expression of a TRβ mutant gene with the 10th exon containing the dominant-negative PV mutant of TRβ (88, 91). Mice that are maintained in the euthyroid status have decreased cardiac contractile function and heart rate. These findings indicate that although TRβ is expressed at much lower levels in all regions of the heart than TRα1, expression of the strong dominant-negative TRβ PV mutant results in decreased contractile function and heart rate.

G. TH analogs

The recognition that there are multiple TRs and that their tissue distribution differs has provided impetus to the long-sought goal of finding TH analogs with different potency in different tissues. In older studies, one analog, T_4, proved to be as active in stimulating cardiac function as in lowering

serum cholesterol concentrations, which may have been due to contamination with L-T_4 (92). Another analog, triiodothyroacetic acid, did seem to have more potent hepatic and skeletal actions than cardiac actions (93). Cardiac tissue contains relatively more TRα, whereas the liver contains more TRβ. The structure of the T_3-binding region of TRβ1 and -β2 is the same, but that of TRα1 is slightly different, making it possible to design ligands that preferentially activate TRα or the two isoforms of TRβ. Little is known about the transcriptional and physiological effects of thyromimetic ligands that preferentially interact with these isoforms.

One of the first TH-related analogs leading to improved contractile function in failing hearts without an increase in heart rate was 3,5-diodothyro propionic acid (94). In addition, reports indicate that Tetrac as well as Triac have a more favorable action on TSH suppression *vs.* inducing cardiac hypertrophy than T_3 does (95, 96).

The TRβ preferred agonist GC-1 is a T_3 analog in which methyl groups replace the iodine atoms of the inner ring and an isopropyl group replaces the iodine atom on the outer ring. The affinity of GC-1 for the α-isoforms of the receptor is 10 times less than for the β1 isoform. The cardiac and hepatic actions of GC-1 were compared with those of T_3 in hypothyroid mice and in normal rats with diet-induced hypercholesterolemia (97). In hypothyroid mice given T_3 or GC-1 for 4 wk, T_3 increased heart rate and cardiac contractility more than did equimolar amounts of GC-1. It was also more potent in raising the myocardial content of the mRNAs for MHCα and -β, SERCa, and HCN2, a cardiac peacemaker channel. In these latter actions, T_3 was nine times more potent than an equimolar amount of GC-1. T_3 had a larger positive inotropic effect than GC-1. T_3, but not GC-1, normalized heart and body weights and mRNAs of both MHC-α and -β as well as SERCa2. In contrast, in these mice, T_3 and GC-1 were equipotent in lowering serum cholesterol concentrations, and GC-1 was more potent in lowering serum triglyceride concentrations. In hypercholesterolemic rats given T_3 or GC-1 for 7 d, the dose of GC-1 needed to lower serum cholesterol concentrations was approximately 10 times higher that that of T_3, and the dose needed to lower serum TSH concentrations by 30% was approximately 20 times higher. In contrast, the dose of GC-1 needed to increase the heart rate by 15% was greater than 120 times higher. As compared with T_3, the tissue to plasma ratio of GC-1 was slightly lower in the liver and much lower in the heart, indicating preferred liver uptake and much less cardiac uptake of GC-1 in comparison with T_3. In conclusion, the T_3 analog GC-1 lowered serum lipid concentrations more effectively than it stimulated cardiac function, indicating that its ability to activate TR isoforms differs from that of T_3. Part of the liver preferred effect may also be due to increased hepatic *vs.* cardiac uptake of GC-1. Thus, distinct T_3R isoform specific cardiac effects allow for development of novel T_3 analogs not resulting in heart rate increases, but efficiently lowering lipid levels. Recently, a TRα agonist termed "KB-141" was developed that binds human TRβ with a 14-fold higher affinity than TRα (98). Administration of KB-141 to primates resulted in significant reduction of body weight and lowered cholesterol (98).

H. Interactions between THs and the sympathoadrenal system

Sympathomimetic agents and TH lead to similar cardiac symptoms, especially inducing tachycardia and increasing the force and velocity of cardiac contraction. Treatment of hyperthyroid patients with sympatholytic agents ameliorates rate-related cardiac changes. These observations have resulted in the hypothesis that some T_3 effects are mediated by an increased activity of the sympathoadrenal system or an increased responsiveness and sensitivity of cardiac tissue to normal sympathomimetic stimuli (99). Plasma and urine levels of catecholamines have been reported as normal (100) or decreased (101) in thyrotoxicosis. These findings contributed to the hypothesis that the thyroid status leads to an increased sensitivity of the sympathoadrenal system. The enhanced sympathetic sensitivity of the hyperthyroid heart may be mediated by an increased number of β-adrenergic receptors (102–104). In addition, an increased level of other components of the sympathetic transmission system occurs. Specifically, investigations in hyperthyroid pigs show that T_3 markedly increases the amount of stimulatory guanine nucleotide-regulatory protein (105). Studies of the various components of the adrenergic-receptor complex in plasma membranes have also shown that β-adrenergic receptors and Gs proteins are up-regulated by TH (103, 105). In contrast, transcripts for types V and VI adenylate cyclase were unchanged by the thyroid status (106). It should be noted that some studies (107) concluded that the adrenergic responsiveness is unaltered by the thyroid status. In a very recent study, the human type 2 iodothyronine deiodinase was expressed in mouse cardiac myocytes, resulting in increased local T_3 production. These mice have decreased expression of inhibitory G protein Giα-3 and increased cAMP accumulation (108). This could result in increased β-adrenergic responsiveness. In contrast, in another recent report, using mice with deletion of three known β-receptors, cardiovascular effects of hyperthyroidism were found in KO mice similar to those of wild-type mice (109), indicating that sensitization of the sympathetic system does not contribute to the cardiovascular effect of hypothyroidism. Cardiac tissue contains both β1- and β2-adrenergic receptor subtypes (110). In most species studied, the β1-receptors account for 70% of total β-adrenergic receptors. Furthermore, β-adrenoceptors are increased approximately 2-fold in the sinoatrial node compared with their level in surrounding myocytes (111). The proportion of β-adrenoceptors in the sinoatrial node is comprised predominantly of β1-receptors (75%). In contrast, β2-receptors are the predominant species in nonmyocyte vascular cells (75%). Thus, β1-receptors are the predominant β-adrenoceptors in cells of myocyte origin and might be responsive to T_3 regulation. Indeed, there appears to be a differential induction of cardiac β1- and β2-adrenergic receptor mRNA in rat myocytes by T_3 (112). T_3 causes a 4-fold induction of cardiac β1-adrenoceptor mRNA, but no significant change in β2-receptor mRNA. The effects of T_3 on β1-adrenergic gene transcription occur within 30 min, with elevations lasting for 72 h. Following the rise in β1-mRNA, there is a 3-fold increase in the density of cardiac β1-receptors, which persists for 48 h. T_3 mediates this effect by the T_3-TR complex binding

to a TRE (113). In contrast, β2-receptors are not significantly increased after T_3 administration. These studies suggest that in cardiac tissue, the β1-adrenoreceptor gene is sensitive to T_3, whereas the β2-receptor gene is influenced minimally. Extrapolation of these animal and *in vitro* studies to the human heart is premature because cardiac β1-receptor gene regulation by T_3 in hypothyroid humans has not been studied. However, the cardiac β2-adrenoreceptor in myxedema may be refractory to T_4 therapy as determined by PCR amplification of the β2-mRNA in cardiac tissue from a hypothyroid subject before and after therapy (53).

I. TH effects on the systemic vascular system

Thyroid disease produces characteristic changes in cardiovascular hemodynamics (114, 115). They arise from effects of T_3 both on the heart and on the systemic vasculature. Thyrotoxicosis may be associated with as much as a 50% decline in systemic vascular resistance (Fig. 2), and T_3 is capable of causing rapid relaxation of vascular smooth muscle cells in culture (116, 117). Because the vascular smooth muscle of resistance arterioles primarily determines peripheral vascular tone, T_3 may directly regulate vascular resistance, which, in turn, causes alterations in blood pressure and cardiac output (118–121). This postulate is supported by another study in which a significant decrease in cardiac output after administration of phenylephrine to hyperthyroid, but not to normal, subjects was noted (119). The ability to block the elevated cardiac output by pharmacologically reversing the changes in vascular resistance of thyrotoxicosis reinforces the possibility that many of the cardiovascular changes of hyperthyroidism occur in response to changes in peripheral tissues. Thyrotoxicosis markedly increases oxygen consumption in the periphery and increases metabolic demands, which require increased blood supply and pumping action of the heart. Changes in vascular resistance are not related to changes in plasma concentrations of the endothelial hormones adrenomedullin and endothelin-1, but altered secretion of the atrial natriuretic peptide and the adrenergic tone may contribute to the T_3-induced changes in vascular resistance (122, 123).

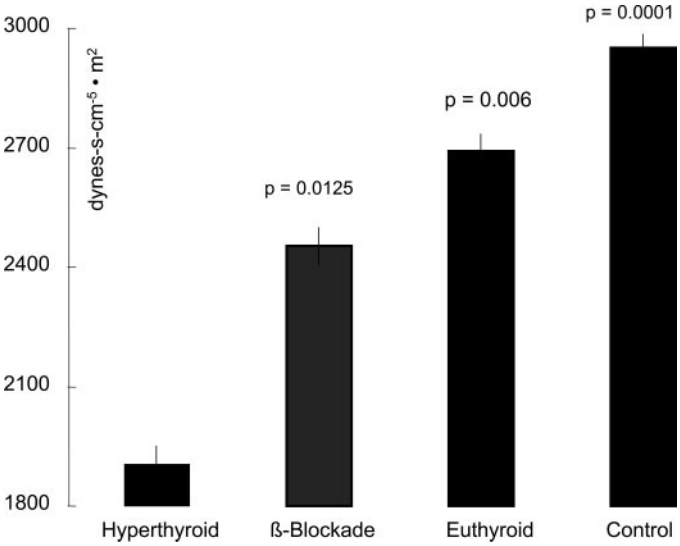

FIG. 2. Systemic vascular resistance index at rest in untreated patients with hyperthyroidism, during β-blockade monotherapy, after restoration of euthyroidism with antithyroid drugs, and in age- and sex-matched, healthy control subjects. Data are shown as mean values ± SEM. [Derived from Ref. 278.]

This hemodynamic effect of T_3 in the periphery markedly contributes to the increased cardiac contraction. Studies using heterotopic cardiac isographs have shown that T_3-induced changes in protein synthesis and cardiac growth primarily result from secondary changes in cardiac work (123). In contrast, T_3-induced changes in myosin isoenzyme predominance occur to the same extent in the heart *in situ* and in the heterotopic isographs (123–126). Thus, T_3-induced hemodynamic effects originating in the periphery may influence increases in total protein synthesis and cardiac hypertrophy.

In hyperthyroid animals, arterial resistance decreases and venous tone increases, leading to an augmented return of blood to the heart (120). The effects of T_3 on venous compliance and blood volume displayed in hyperthyroid calves include an increase in mean circulatory filling pressure, no change in blood volume, and a decrease in venous compliance, whereas hypothyroid animals showed a decrease in mean circulatory filling pressure and blood volume but no change in venous compliance.

In contrast, myxedema is characterized by a low cardiac index, decreased stroke volume, decreased vascular volume, and increased systemic vascular resistance. Total blood volume is decreased in hypothyroidism and varies directly as a function of basal metabolism rate. Renal perfusion, when measured by glomerular filtration, is also decreased. Although sodium excretion is normal, free water clearance is impaired and can lead to hyponatremia. Total-body albumin distribution is expanded in myxedema, in keeping with the development of high-protein effusions in many body cavities (127).

Thyroid dysfunction alters blood pressure: hyperthyroidism has only minor effects on mean arterial blood pressure, because increases in systolic pressure, caused by increased stroke volume, are offset by decreases in diastolic pressure, due to peripheral vasodilatation (128–130). Conversely, hypothyroidism is associated with increases in diastolic pressure. In a study of 40 hyperthyroid patients, overtreatment that resulted in myxedema was associated with an increase in diastolic pressure that was reversible when thyroid function returned to normal. In a survey of 688 consecutive hypertensive patients, 3.6% were found to be hypothyroid, and in this subset, diastolic blood pressure fell significantly after adequate T_4 replacement, suggesting a cause-and-effect relationship (128, 129). Renin, angiotensin, and aldosterone play a minor role in this form of hypertension (131).

J. Presence of functional TSH receptor (TSH-R) in cardiac muscle

Recently, functional TSH-R was demonstrated in human heart and in cultured mouse cardiomyocytes (132). Furthermore, a case of Graves' disease in a 25-yr-old man, who

developed cardiomyopathy with severe heart failure, was reported. Pathological examination of the myocardial biopsies showed fibroblast infiltration and degenerative changes. After the cardiomyopathy subsided, the patient developed goiter and ophthalmopathy, suggesting a common pathogenesis for the cardiomyopathy and thyroid-associated orbitopathy (133). Using RT-PCR and DNA sequencing, TSH-R mRNA was identified in the patient's heart. These findings question the traditional concept of TSH and TSH-R antibodies as exclusively acting on thyroid tissue. Already, the possible actions of TSH-R autoantibodies on specific TSH-R in orbital tissue provide interesting evidence for a mechanism in ophthalmopathy associated with Graves' disease (134). Thus, binding of TSH-R autoantibodies to cardiac TSH-R may be directly involved in this pathology. Taken together, these data indicate that autoimmunity against the TSH-R may contribute to both the cardiomyopathy and ophthalmopathy in similar cases of Graves' disease.

III. Molecular Effects of Amiodarone in the Heart

Amiodarone is an iodine-rich benzofuran derivative and an effective drug against a wide range of cardiac arrhythmias. Approximately 37% of amiodarone (by weight) is organic iodine; 10% of the latter is deiodinated to yield free iodine. A maintenance dose of 0.2 g/d results in a daily intake of organic iodide of 0.075 g. In patients treated with amiodarone, urinary and plasma levels of inorganic iodide increase 40-fold, whereas thyroid iodide uptake and clearance decrease significantly. Therefore, TH dynamics change in almost all patients receiving amiodarone (135–139). The electrophysiological effects on cardiac muscles seen with long-term administration may be mediated by amiodarone itself, its active metabolite desethyl-amiodarone, or both. Amiodarone shares some structural analogies with THs, and its cardiac effects are similar to hypothyroidism in many aspects (140). Amiodarone induces bradycardia, lengthening of the cardiac action potential, and depression of myocardial oxygen consumption. It has been suggested, therefore, that amiodarone may induce a local hypothyroid-like condition in the heart via several possible mechanisms: 1) an inhibition of the peripheral conversion from T_4 to T_3 by 5′-deiodinase; 2) an inhibition of transport of T_4 and T_3 through the cell membrane; 3) an inhibition of T_3 binding to nuclear receptors; and 4) down-regulation of TR isoforms (136, 139).

Recent data also suggest that long-term treatment with amiodarone may antagonize T_3 at a cellular level and thereby counteract its hormonal effects on the electrophysiological properties of cardiac muscle (Ref. 141 and Table 4). Amiodarone, however, also has electrophysiological effects independent of the TH system. Amiodarone's antiarrhythmic effects cover all classes from I–IV. The duration of cardiac action potential is viewed as a postreceptor effect of nuclear T_3 receptors in the heart. Receptor occupancy is decreased in hypothyroidism and in amiodarone-treated patients, resulting in an identical lengthening of the action potential (140). Amiodarone has no direct effect, independent of T_3, on cardiac β-adrenoceptors, but amiodarone may inhibit the T_3-induced increase in receptor density (142, 143). At low T_3 concentrations, amiodarone decreases the efflux rate of internalized β-adrenoreceptors to the cell surface, presumably via an extranuclear action of the drug on membranes, whereas at higher T_3 concentrations, amiodarone decreases synthesis of β-adrenoceptors via a genomic action of the drug on the T_3-responsive gene encoding for the β-adrenergic receptor (143).

TABLE 4. Amiodarone and the heart

Molecular aspects
↓ Nuclear thyroid hormone (T_3) receptor occupancy
Inhibition of T_3-induced increase in cardiac β-adrenoreceptor density
Changes in gene expression of α (↓) and β-MHC (↑) ⇒ myosin isoenzyme shift V1 → V3
↓ Calcium ATPase activity of myosin
Clinical aspects: local hypothyroidism-like condition
↓ Heart rate
↓ Myocardial oxygen consumption
↓ Myocardial contractility
↑ Cardiac action potential

In animal hearts (pigs) treated with amiodarone, the maximum binding capacity of β-receptors and calcium channels is reduced. The maximum binding capacity for T_3 is unchanged, suggesting that no functional reduction in the number of T_3 receptors occurs. However, desethyl-amiodarone competitively inhibits the binding of T_3 to TRα1 but acts as a noncompetitive inhibitor to T_3 binding to TRβ1, and this action may be responsible for the local hypothyroid-like effects. In a comparison of rats with normal thyroid function and those that had thyroidectomy, amiodarone reduced cardiac β-receptor density and heart rate in the former but not the latter group. This finding implies that a minimum serum TH level is necessary for the drug to produce some of its cardiac effects. These changes occur independently of alterations in thyroid secretion and serum T_3 levels. Exogenous T_3-mediated increase in β-receptor density and heart rate is also partly inhibited by amiodarone. These observations suggest that the lowering of β-receptor density by amiodarone is related to T_3 antagonism at the cardiac cellular level.

In amiodarone-treated rats a shift from the myosin isoenzyme V1 to V3 is seen, although the decrease is less than in hypothyroid animals. The changes are found in mRNA and protein levels, and the effect of amiodarone is abolished by the addition of T_3 (144, 145). The effect of amiodarone is also smaller when given to hypothyroid animals, again suggesting that the effect is T_3 dependent. The Ca^{++}ATPase activities of myosin also decrease in hearts of amiodarone-treated rats, although to a lesser extent than in hearts of hypothyroid rats; the effect of amiodarone is abolished by T_3. Furthermore, the acute increase in cardiac performance (146) in response to iv T_3 is blunted in pigs pretreated with amiodarone. The data indicate that amiodarone impairs myocardial contractility through hypothyroid-like changes in the gene expression of α- and β-MHC. This genomic effect seems to be dependent on T_3. Finally, amiodarone therapy increases the number of voltage-operated Ca^{++} channels in rat heart membranes (147); the effect is smaller but otherwise similar to that observed in myxedema.

TABLE 5. Cardiovascular features

Physical examination	Hemodynamic changes	ECG/x-ray/ultrasound
Hyperthyroidism		
Tachycardia at rest	↑ Cardiac output	↓ QT interval
↑ Pulse amplitude	↑ Myocardial contractility	↓ PR interval
Systolic murmur	↑ Systolic/diastolic function	ST segment elevation
Mitral valve prolapse	↑ Systolic blood pressure	Atrial fibrillation
↑ First heart sound	↑ Blood volume	Wolff-Parkinson White Syndr
Possible third heart sound	↑ Venous resistance	↓ Contraction times
Ankle swelling	↓ Arterial resistance	Cardiac hypertrophy
Unspecific symptoms (palpitations, shortness of breath, chest pain)	↓ Diastolic blood pressure	Heart block
Means-Learman "scratch"	↓ ↓ Circulation time	
Hypothyroidism		
Bradycardia	↓ Cardiac output	↑ QT interval
Weak pulse	↓ Stroke volume	↑ Conduction abnormalities
Hypertension	↓ Myocardial contractility	T-wave inversion
Faint heart sounds	↓ Blood volume	Atrioventricular block
Quiet precordial findings	↑ Diastolic blood pressure	Pericardial/pleural effusions
↓ Exercise tolerance	↑ Peripheral vascular resistance	Cardiac tamponade (rare)
Dyspnea on exertion	↑ Circulation time	Ascites
Congestive heart failure	Signs of peripheral vasoconstriction	
Ankle swelling		

IV. Hyperthyroidism and the Heart

A. Cardiovascular symptoms and signs in hyperthyroidism

Cardiac symptoms are common in hyperthyroid patients (Refs. 148–150, Table 5, and Fig. 2). One can distinguish between chronotropic alterations, which are manifested by sinus tachycardia, AF, and shortened PR intervals, and inotropic alterations, which reflect changes in the systolic contractile behavior of the heart (*e.g.*, increased cardiac index, stroke volume, and velocity of wall shortening, as well as decreased ejection period and lusitropic effects related to diastolic relaxation of the heart) (Fig. 3). Alterations in the pulse and heart tones, as well as Means-Lerman "scratch" may also be observed in hyperthyroidism. In addition, rare reports of heart block in Graves' disease should be mentioned (148).

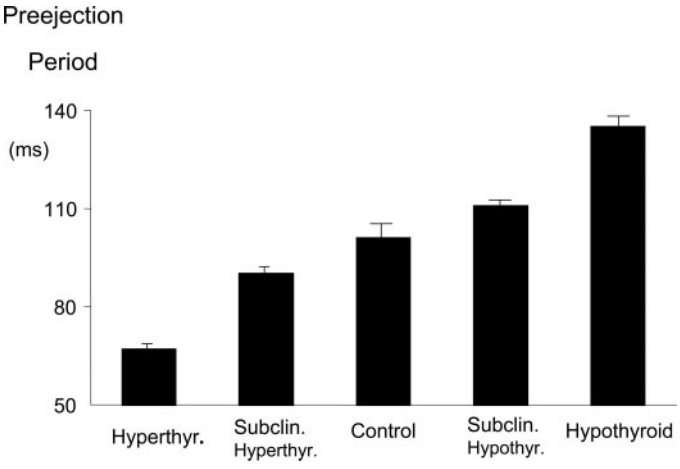

FIG. 3. Effects of thyroid hormones on cardiac contractility. The PEP, a noninvasive cardiac ultrasound parameter for cardiac contractility, has been measured [milliseconds (ms)] in healthy, euthyroid, age- and gender-matched controls, and in both patients with overt and subclinical hyper- and hypothyroidism, respectively. Data are shown as mean values ± SEM, Kruskal-Wallis Test, $P < 0.0001$. [Derived from Refs. 152, 227, 276, and 278.]

Patients with hyperthyroid heart disease frequently complain about symptoms related to chronotropic alterations. They often experience palpitations, as well as an irregular and vigorous heart beat. In addition, severely hyperthyroid patients can exhibit signs of congestive heart failure in the absence of prior cardiac pathology (148). The frequent occurrence of cardiac manifestations in hyperthyroid patients can be the result of thyrotoxicosis itself, underlying heart disease that decompensates further by hyperthyroidism-induced increased demand on the heart, or increased occurrence of specific cardiac abnormalities. Detailed examinations indicate that cardiac output in vigorously exercising patients decreases (151, 152). This change is not reversible by β-receptor blockade and can only be eliminated by treating the underlying thyrotoxicosis. In addition, hyperthyroid patients frequently complain of dyspnea on exertion even in the absence of cardiac failure. Because hyperthyroidism leads to a weakening of skeletal and intercostal muscles, dyspnea may be related more to a weakness of respiratory muscles than to cardiac abnormalities themselves (5). In children, congestive heart failure may occur in severe thyrotoxicosis, but symptoms completely disappear after normalization of TH values. These reports give credence to the occurrence of decreased cardiac pump function in the absence of underlying cardiac disease. In this respect, nonspecific changes, such as necrosis of isolated myocytes of increased size, small areas of fibrosis, an increased number of mitochondria or round-cell infiltration, can be identified only on histological examinations of hearts obtained from hyperthyroid patients (153–155).

To determine the influence of age on signs of thyrotoxicosis, 880 hyperthyroid patients were prospectively examined and compared with euthyroid controls (156, 157). Many signs showed little change until after the fifth decade of life when they began to decrease gradually. Findings that increased with age were AF and weight loss. In a subgroup aged 60–83 yr, palpitations and tachycardia had a true-positive rate of 51% and a false-positive rate of 9%. In another paper (158), prevalence of cardiovascular symptoms and

signs in 85 patients older than 60 yr with thyrotoxicosis was reported. Symptoms included dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea in 66%, palpitations in 42%, and angina pectoris in 20%. With respect to cardiac signs, a heart murmur was noted in 69%, a heart rate of at least 100 beats/min in 58%, an AF in 45%, and a cardiomegaly in 11%. T-wave and ST-segment abnormalities were present in 62 and 57%, respectively. Furthermore, comparison of classical signs of hyperthyroidism between patients aged 70–90 yr and younger patients (23–50 yr) was done (159), and older patients were also compared with controls (mean age, 81 yr). Three signs were found in more than 50% of older patients: tachycardia, fatigue, and weight loss. Only AF (35 *vs.* 2%) and anorexia (32 *vs.* 4%) were found more frequently in older people. Comparison with older controls showed two signs that were highly associated with hyperthyroidism in older people: tachycardia (odds ratio, 11.2), and apathy (odds ratio, 15).

B. Cardiac arrhythmias

1. Electrophysiological background and experimental data. THs exert marked influences on electrical impulse generation (chronotropic effect) and conduction (dromotropic effect). T_3 increases the systolic depolarization and diastolic repolarization rate and decreases the action potential duration and the refraction period of the atrial myocardium as well as the atrial/ventricular nodal refraction period. In a double-heart model, T_4 increased similarly the heart rate of the enervated infrarenal and the innervated *in situ* hearts (123). *In vitro* studies found that T_3 decreases the duration of the repolarization phase of the membrane action potential and increases the rate of the diastolic repolarization and therefore the rate of contraction (160–162). The mechanism by which T_3 induces the electrophysiological changes is related in part to its effects on sodium pump density and enhancement of Na^+ and K^+ permeability (163). Heart rate effects are mediated by T_3-based increases in the pacemaker ion current if in the sinoatrial node as mentioned above. The L-type calcium channel 1D, which also serves as an important pacemaker function, is also increased by T_3.

Studies using an isolated heart model found that hearts from animals with experimental thyrotoxicosis show increased heart rates and shorter mean effective refractory periods than hearts from euthyroid animals (164). In both thyroidectomized and hypophysectomized rats, the heart rate decreased similarly and proportionally to T_3 levels (164). In the same study, the effects of thyroidectomy and chemical sympathectomy on the heart were compared. The group with thyroidectomy had a significantly slower heart rate than the group with sympathectomy. However, both groups responded with a similar increase in heart rate after treatment with T_3, suggesting a direct chronotropic effect of T_3.

2. Clinical studies in humans. In humans, chronotropic effects of THs have been assessed using 24-h ECG recordings. Hyperthyroid patients show an increase in heart rate throughout sleeping and waking hours (165), whereas in hypothyroid patients a decrease in basal, average, and maximal heart rates was found although most of them were not bradycardic at rest. After treatment, heart rates in both groups returned to normal (165). In a prospective trial, the arrhythmia profile was analyzed in hyperthyroid patients, before, during, and after antithyroid therapy (166). The number of patients with atrial premature complexes was elevated compared with controls (88 *vs.* 30%) and decreased markedly after therapy. Prevalence of atrial arrhythmia was age related before as well as during antithyroid treatment. Ventricular arrhythmias were present in 29% of the patients with toxic nodular goiter (median age, 59 yr) in contrast to only 3% of the cases with Graves' disease (37 yr). In another study (167), the efficacy of the calcium channel-blocking drug diltiazem in lowering the incidence of arrhythmias was evaluated. Heart rate and the number of ventricular premature beats significantly decreased but returned to baseline values after diltiazem was discontinued. In a further paper (164), circadian rhythm of heart rate was maintained in thyrotoxicosis, although heart rate variability was significantly increased, supporting the view that normal adrenergic responsiveness persists in thyrotoxicosis. The prevalence of premature atrial contractions was not different before and after therapy. In conclusion, ventricular arrhythmias are rare in hyperthyroid patients without cardiac disease. Their prevalence remains essentially unchanged during antithyroid therapy and is comparable to that of a normal population. Antiarrhythmic therapy is definitely not necessary in these patients.

3. AF. From a clinical viewpoint, the most important electrocardiography abnormality in thyroid disease is AF. AF is a recognized manifestation of hyperthyroidism. The rapid and irregular heartbeat produced by AF increases the risk of blood clot formation inside the heart, which eventually become dislodged, causing embolism, stroke, and other disorders. This arrhythmia, usually persistent rather than being paroxysmal, occurs in 2–20% of hyperthyroid patients overall, and hyperthyroidism accounts for 5–15% of all patients with newly diagnosed AF. This rhythm disorder is significantly more common in older patients, reflecting a reduction in the threshold for fibrillation with age, later diagnosis, and an increase in the prevalence of coexistent ischemic and degenerative heart disease (168, 169). In one series, 25% of hyperthyroid patients older than 60 yr had AF compared with a 5% prevalence in patients less than 60 yr (170). Patients with toxic nodular goiter also showed, because of their old age, an increased prevalence of AF (43%) *vs.* 10% only in younger patients with Graves' disease. Also, analysis of rhythm disorders in 219 patients with hyperthyroidism (171) showed an age-dependent distribution of AF and sinus node dysfunctions. Furthermore, to study the relationship between left atrial size and AF in hyperthyroidism, 92 patients with Graves' disease were examined (172). Nineteen (21%) had fibrillation; 31% of the patients older than 40 yr had fibrillation but none of those younger than 40. Left atrial enlargement existed in 7% of patients younger than 40 yr, in only 2% of those older than 40 without fibrillation, and in as many as 94% of those older than 40 yr with AF. In contrast, a large study found that less than 1% of cases of new-onset AF were caused by overt hyperthyroidism. Therefore, although serum TSH should be measured in all patients with new-onset AF to rule out thyroid disease, this association is

rather uncommon in the absence of additional symptoms and signs of hyperthyroidism (173).

Low TSH is a risk factor for later development of AF (174). In the Framingham study, more than 2000 clinically euthyroid subjects who were older than 60 yr and in sinus rhythm were followed to determine the frequency of AF over the next 10 yr. The cumulative incidence of AF was 28% among subjects with low TSH (<0.1 mU/liter) and 11% among subjects with normal values. Overt hyperthyroidism (but not AF) subsequently developed in two people with low TSH and one with normal TSH. After adjustment for other risk factors, the relative risk of fibrillation in the subjects with low TSH was 3.1. Two thirds of the low TSH subjects were being treated with T_4; however, excluding these subjects had little effect on the relative risk of fibrillation associated with low TSH. Mean T_4 concentration was slightly higher in the low TSH group but was within the normal range in 84% of those not receiving T_4 replacement and was not correlated with the subsequent occurrence of AF.

In a large study including more than 23,000 persons, AF was present in 513 persons (2.3%) in the group with normal values for serum TSH, and in 78 (12.7%) and 100 (13.8%) in the groups with subclinical and overt hyperthyroidism, respectively (175). The prevalence of AF in patients with low serum TSH concentrations (<0.4 mU/liter) was 13.3% compared with 2.3% in patients with normal values for serum TSH ($P < 0.01$). The relative risk of AF in subjects with low serum TSH and normal free T_3 and free T_4 concentrations, compared with those with normal concentrations of serum TSH, was 5.2 [95% confidence interval (CI), 2.1–8.7; $P < 0.01$]. Thus, a low serum TSH concentration is associated with a more than 5-fold higher likelihood for the presence of AF with no significant difference between subclinical and overt hyperthyroidism.

Regarding the high incidence of AF in older patients with thyrotoxicosis, it is important to detect thyroid dysfunction in all subjects over 60 yr of age. Once euthyroidism is restored, all patients who revert to sinus rhythm (~60%) spontaneously do so within 4 months of being euthyroid (176). In addition to age, the main determinant of reversion to sinus rhythm appears to be the duration of AF: patients who had been in AF for more than 1 yr and those who are older are likely to need intervention in the long run, probably reflecting the coexistence of intrinsic heart disease in these hyperthyroid patients with AF (177).

C. Heart failure and cerebrovascular events in hyperthyroidism

Severe complications of thyrotoxicosis arise from cardiovascular involvement: tachyarrhythmias, associated thromboembolism, and heart failure. Cardiac decompensation is more prevalent in hyperthyroid patients with advancing age (158, 159). In the older patient, symptoms of overt heart failure or exacerbation of symptoms of an established cardiac disease may be dominant. In older patients with underlying coronary artery disease, angina pectoris can occur simultaneously with the onset of hyperthyroidism, because of an increase in myocardial oxygen demand, especially if tachycardia is present. Tachycardia also reduces the time in diastole for coronary perfusion, decreasing myocardial oxygen supply. The presence of ischemic or hypertensive heart disease may compromise the ability of the myocardium to respond to the metabolic demands of hyperthyroidism. Myocardial oxygen utilization increases about 34% per unit mass of myocardium in the average hyperthyroid patient (10). Hyperthyroidism may also cause angina pectoris in patients with normal coronary arteries (178). In elderly patients with apathetic hyperthyroidism, AF or congestive heart failure may be the only clinical manifestation of thyrotoxicosis. Heart failure frequently develops in hyperthyroid patients with AF, mainly because a rapid ventricular rate impairs diastolic filling and cardiac performance but possibly also from abnormal intrinsic LV performance. Multiple factors, *e.g.*, the high cardiac output state and increased myocardial oxygen demand, the decreased LV contractile reserve and reduced LV filling because of the loss of atrial contribution, and finally the rapid ventricular rate, all contribute to the development of congestive heart failure in patients with severe and untreated hyperthyroidism. Thus, prompt recognition and effective management of cardiac as well as other organ-system manifestations of thyrotoxicosis in patients over 50 yr of age are important, because cardiovascular complications are the chief cause of death after treatment of hyperthyroidism (179–181).

Thyrotoxic AF is complicated by thromboembolism in approximately 15% of cases (182). Of 31 deaths over 10 yr with a primary diagnosis of hyperthyroidism, AF was documented in 61%, and 26% presented with a major arterial embolus (183). In a large collective of 262 patients with thyrotoxicosis and AF, 26 (10%) episodes of arterial embolism were noted (184). Three patients in this series were younger than 55 yr at the time of the embolic event, whereas 13 were older than 65 yr. In another paper, arterial embolism was noted in 12 of 30 hyperthyroid patients in AF, compared with no embolic episodes in 121 patients in sinus rhythm (185). The risk of embolism was higher in older patients, in males, and in those with coexisting hypertensive heart disease.

The risk of cerebrovascular events, with special attention to the first year after the diagnosis of hyperthyroidism, was retrospectively studied in 610 patients with initially untreated thyrotoxicosis, 91 (15%) of whom had AF, with the highest frequency in the elderly patients (186). In 46% of the patients with fibrillation, sinus rhythm developed after treatment of hyperthyroidism, but the frequency of reversion to sinus rhythm varied from 100% in the youngest patients to 25% in the elderly. A total of 27 (4.4%) cerebrovascular events occurred, 12 (13%) in those having fibrillation and 15 (3%) in patients with sinus rhythm. Thirteen patients had stroke and 14 had transient ischemic attack. There were significantly more strokes in patients with fibrillation compared with those in sinus rhythm. Age only was an important risk factor whereas fibrillation was not significant as an independent risk factor. From this study, the indication for prophylactic treatment with anticoagulants for prevention of stroke in thyrotoxic AF seems doubtful, especially because no controlled studies of such treatment in patients with fibrillation are currently available. Thus, whether hyperthyroid patients with AF should receive anticoagulant therapy is controversial. Nevertheless, in elderly patients with thyrotoxic AF, the

risk of arterial thromboembolism warrants the consideration of anticoagulant therapy (Table 6). Prophylactic warfarin therapy reduces the frequency of embolic events in patients with fibrillation in general, but it also entails a finite risk of hemorrhagic complications that may exceed the risk of thromboembolism, especially in the elderly. Because increased sensitivity to warfarin in hyperthyroidism has been observed, the loading dose should, therefore, be reduced and therapy monitored closely (187–189).

D. Cardiovascular morbidity and mortality in hyperthyroidism

There have been few population-based studies examining the long-term influence of thyroid disease and its treatment on morbidity and mortality. In a cohort of 7209 hyperthyroid subjects treated with radioiodine, the underlying cause of death for the cohort was recently compared with age-specific mortality data for England and Wales (179, 190). The standardized mortality ratio (SMR) was used as a measure of relative risk. During a period of follow-up of 105,028 person years of risk, 3,611 subjects died, the expected number of deaths being 3,186 ($P < 0.00001$). This excess mortality was largely accounted for by an excess of deaths caused by circulatory diseases, both cardiovascular (SMR 1.2, 95% CI, 1.2–1.3; $P < 0.001$); and cerebrovascular (SMR 1.4, 95% CI, 1.2–1.5, $P < 0.001$). Rheumatic (SMR 3.2, 95% CI, 2.5–4.2; $P < 0.001$) and hypertensive heart disease (SMR 2.1, 95% CI, 1.6–2.7; $P < 0.001$) had the highest mortality ratios, followed by deaths secondary to dysrhythmias (SMR 1.8, 95% CI, 1.5–1.9; $P < 0.001$). This excess mortality was most evident in the first year after radioiodine treatment and declined thereafter. Excess deaths as a result of hypertensive and other forms of heart disease were confined to those ages 50 yr or older; this reflects increasing mortality from heart disease with increasing age and exacerbation of these disorders by hyperthyroidism.

Also, excess deaths as a result of circulatory diseases were reported in 1762 hyperthyroid women treated with radioiodine and followed for an average of 14 yr [SMR 1.4, 95% CI 1.3–1.6 (191)]. Another study of 10,552 hyperthyroid subjects followed for an average of 15 yr after radioiodine treatment further described an excess vascular mortality (192). It is likely that dysrhythmias may have contributed to the excess mortality from both cardiovascular and cerebrovascular disease, especially in those with AF in whom predisposition to embolic events is well described; this risk is highest in those over the age of 75 yr. Supraventricular premature complexes are known to initiate AF, particularly those originating in the pulmonary veins (193), and TH increases the automaticity of pulmonary vein myocytes (194). This suggests continuing arrhythmic substrate despite restoration of biochemical euthyroidism and effects on myocardial electrical remodeling, especially of the atria, by THs.

TABLE 6. Predictors of thromboembolic stroke in patients with atrial fibrillation

- Rheumatic mitral stenosis
- Prior arterial thromboembolism
- Prior myocardial infarction
- Recent congestive heart failure
- Echocardiographic left ventricular dysfunction
- Echocardiographic left ventricular hypertrophy
- Echocardiographic left atrial enlargement
- Systemic hypertension
- Mitral annular calcium
- Prolapse of myxomatous cardiac valve
- Age

Increased cardiac and cerebrovascular mortality has also been recently described in a community-based review of subjects with low TSH followed over a 10-yr period (195). The cohort consisted of 1191 subjects aged 60 yr and over who were not receiving T_4 therapy or antithyroid medication. A serum TSH concentration was measured at baseline. Mortality from all causes was found to be significantly increased at 2, 3, 4, and 5 yr after initial measurement in those with a low serum TSH concentration (< 0.5 mU/liter) compared with the expected mortality for the control population of England and Wales. The SMR values (95% CI) were 2.1 (1.0–4.5), 2.2 (1.2–4.0), 1.9, and 2.0 at yr 2, 3, 4, and 5, respectively. This increase in all-cause mortality was largely accounted for by significant increases in mortality because of circulatory diseases. Comparison of those with low TSH and the remainder of the cohort also confirmed significant increases in vascular mortality between yr 2 and 5. Nevertheless, these conclusions should be tempered by the fact that the definition of hyperthyroidism in the British study was a low TSH, with its obvious potential confounding implications of nonthyroidal illnesses.

Therapy for the cardiovascular manifestations of hyperthyroidism includes treatment of the underlying thyroid condition by antithyroid medications, *e.g.*, propythiouracil or methimazole, radioactive iodine treatment, or surgery after a euthyroid status is obtained. Cardiac failure in hyperthyroidism may result, in part, from rapid heart rate-induced failure. Doubling the heart rate of a normal dog by a pacing mechanism leads, after some time, to cardiac failure (196). Decreasing the heart rate by β-sympathetic blockade and/or the use of digitalis can lead to significant improvement in cardiac contractile function. This therapeutic effect also presents an example of the close interconnection between rate-related chonotropic effects and inotropic or contractile changes. Prophylactic anticoagulation therapy (warfarin) is advisable in hyperthyroid patients with AF, especially in older patients with underlying heart disease such as a dilated left atrium or abnormal mitral valves.

E. Subclinical hyperthyroidism

1. Endogenous subclinical hyperthyroidism. Subclinical hyperthyroidism is defined as a below-normal TSH in association with a normal total and free T_4 and T_3 (197). It may be caused by T_4 treatment (exogenous) or by endogenous thyroid disease. Subclinical hyperthyroidism is associated with changes in cardiac performance and morphology (198), but this has not been consistently found in all patient populations (199). Changes include increased heart rate, increased LV mass, increased cardiac contractility, diastolic dysfunction, and the induction of ectopic atrial beats or arrhythmias (175, 200, 201). Increased LV mass in subclinical hyperthyroidism results from chronic hemodynamic overload. Indeed, the car-

diac renin-angiotensin system is activated in hyperthyroidism-induced cardiac hypertrophy (202). LV mass may also be increased because of the effects exerted by THs on cardiomyocyte contractile protein synthesis. LV hypertrophy is associated with increased risk of cardiovascular morbidity and mortality (200, 201). Increase in mass may worsen LV filling in elderly people, in whom cardiac compliance is already reduced because of interstitial fibrosis.

Subclinical thyrotoxicosis is an independent risk factor for the subsequent development of AF. Increased sympathetic tone and THs *per se* increase atrial excitability and shorten the refractory period of the conduction system, thus favoring occurrence of AF and possibly reentrant atrioventricular nodal tachycardia. Also, function and expression of human atrial L-type calcium channels are increased in subclinical thyrotoxicosis (203). It has also been shown that subclinical hyperthyroidism is a risk factor for AF (175).

Subjects with subclinical hyperthyroidism have an increased vascular mortality when followed over a 10-yr period (201). Supraventricular dysrhythmias, particularly AF, in older patients may account for some of the excess cardiovascular and cerebrovascular mortality described. Therefore, subclinical thyroid dysfunction should be treated in a timely manner, especially in patients with cardiac symptoms or disease. Although these assumptions are likely to be true, they remain assumptions at the present time because it has never been proven that restoration of euthyroidism in subclinical hyperthyroidism prevents the development of AF or lowers vascular mortality (201).

The same therapeutic approaches described in the section on therapy for hyperthyroid patients apply to patients with subclinical hyperthyroidism, and treatment has beneficial effects (204). However, specific symptoms must be identified to warrant treatment.

2. Exogenous subclinical hyperthyroidism. Alterations in cardiac hemodynamics have been reported in some, but not all, studies of patients with exogenous subclinical hyperthyroidism (205–208). In one trial (205), hypothyroid subjects treated with L-T_4, having both normal free T_4 and T_3 concentrations but suppressed TSH levels, showed mild but significant changes in myocardial function, thus reflecting "tissue hyperthyroidism" at the cardiac level. Furthermore, subjects on suppressive doses of L-T_4 averaging 0.163 mg/d, had significant changes in systolic time intervals including higher values of LV fractional shortening and rate-adjusted velocity of shortening (206). ECG monitoring demonstrated significant increases in average heart rate and atrial premature beats in the patients compared with controls, and one of the patients had spontaneous episodes of AF. Furthermore, echocardiography analysis showed relevant diastolic dysfunction (208) and an increased LV mass index in patients compared with controls. Marked impairment of cardiac functional reserve and physical exercise capacity were also noted (209). Using a β1-selective antagonist for 6 months in association with the L-T_4 suppressive therapy, the same authors showed that the heart rate normalized and the LV mass was significantly reduced toward normal (210). Interestingly, this therapy did not significantly alter indices of cardiac contractility as fractional shortening and velocity of circumferential fiber shortening. Importantly, the β-adrenergic blockade also decreased atrial premature beats and eliminated the spontaneous AF in the single patient in whom it occurred. Finally, this study utilizing the hyperthyroidism symptom-rating scale score showed that β-blockade significantly improved the patient's sense of "well-being" as well as his/her cardiac performance and exercise tolerance. In another paper (211), long-term TSH-suppressive therapy with L-T_4 was associated with an 18% increase in LV mass index.

Taken as a whole, these studies show that exogenous subclinical hyperthyroidism may have significant effects on cardiac structure and function, increasing heart rate, LV mass, LV contractile function, the prevalence of atrial premature contractions, and the number of hyperthyroid symptoms. Most of these are reversed by β-adrenergic blockade therapy although cardiac contractility remains augmented. These studies emphasize that L-T_4 suppressive therapy has consequences, many of which are clinically relevant. Thus, the clinical recommendation arising from these studies is that patients receiving replacement L-T_4 therapy should be dosed in such a way as to achieve a normal and not suppressed TSH level (212). Furthermore, when L-T_4 suppressive therapy is clinically indicated, β-adrenergic blockade, although rarely employed, may be of benefit.

V. Hypothyroidism and the Heart

A. Cardiovascular symptoms and signs in hypothyroidism

Alterations in the pulse and signs of peripheral vasoconstriction in hypothyroidism may be observed. Rarely, myxedema alone may cause heart failure, typically in patients with severe and prolonged T_4 deprivation. Recent positron-emission tomographic studies of oxygen consumption in patients with myxedema have revealed that myocardial work efficiency is lower than in normal subjects (213). Hypothyroid patients with heart failure *usually* have some form of intrinsic cardiac disease on which T_4 deficiency has been superimposed. In addition to decreased direct effects of T_3 in cardiac myocytes, indirect effects occur through decreases in peripheral oxygen consumption and changes in hemodynamic parameters (7). These changes have already been noted in subjects with short-term hypothyroidism in whom a significant decrease in myocardial contractility and a prolongation of diastolic relaxation could be demonstrated (214).

The widened heart shadow and low electrocardiography voltage that Zondek originally described are attributable, in part, to pericardial effusion, which is echocardiographically demonstrable in hypothyroid patients. Rare reports of pericardial tamponade with myxedematous pericardial effusions should be mentioned. Accumulations of fluid in the pericardial and other serous spaces of patients with myxedema are the result of both increased plasma albumin egress from blood and decreased lymphatic clearance of interstitial fluid proteins (127). Pericardial effusions are seldom hemodynamically significant even when large, presumably because their slow accumulation permits pericardial compliance. The prevalence and size of pericardial effusions have

been correlated with the severity of hypothyroidism; they typically resolve after 2–3 months of T_4 therapy.

No specific pathophysiological changes can be identified that characterize the myxedema heart. The cardiac silhouette is enlarged; however, heart weight is usually normal. Cardiac papillary muscle obtained from hypothyroid animals shows a depression of the force velocity curve and reduced rate of tension development, indicating significant contractile abnormalities. Myofibril swelling with loss of striation and some degree of interstitial fibrosis occurs on histological examination of hypothyroid hearts. In addition, accumulation of mucopolysaccharides can be demonstrated. On electron microscopic examination, mitochondria show disruption and loss of cristae with lipid inclusion (215). In an animal model of ventricular fibrillation, myxedema increased the fibrillate threshold of the ventricles (216). In hypothyroid patients, only atrioventricular blocks, sinus bradycardia, and rare episodes of "torsade de pointes" have been reported. In humans, the prolongation of the QT interval encountered in hypothyroidism is similar to that seen in euthyroid patients on class 3 antiarrhythmic agents. Finally, in patients with myxedema, T_4 replacement therapy did not significantly increase the frequency of benign atrial and/or ventricular premature beats (14).

B. Myxedema and coronary artery disease

Hypothyroidism is related to coronary artery disease in two ways. First, its metabolic and hemodynamic characteristics, *i.e.*, hypercholesterolemia and hypertension, increase the risk of atherogenesis (217, 218). Second, hypothyroidism creates a negative chronotropic and inotropic state in which there is diminished myocardial oxygen demand, and recovery from which may provoke underlying coronary ischemia. The most clinically important consequence of T_4 deficiency on lipoprotein metabolism is elevation of circulating low-density lipoprotein (LDL)-cholesterol concentrations. Hypothyroidism is commonly diagnosed in patients referred for management of hypercholesterolemia. Hypertriglyceridemia and impairment of fatty acid mobilization are also associated with hypothyroidism. The occurrence of increased risk factors contrasts with the relatively low incidence of myocardial infarction or angina pectoris in the hypothyroid patient population. This discrepancy is most likely explained by the decreased metabolic demand placed on the myocardium. Nevertheless, the risk that T_4 therapy of hypothyroidism will exacerbate myocardial ischemia in patients with coronary artery disease is widely appreciated, as is the universal recommendation that T_4 therapy be initiated in a low dose and escalated in small increments in the management of such patients. However, there is little clinical research addressing this issue. Among 55 hypothyroid patients with coronary disease, T_4 and/or T_3 exacerbated heart disease in only nine, whereas the remainder were unchanged or improved (219). Although the increases in heart rate and contractility that occur with T_4 therapy augment myocardial oxygen demands, simultaneous reductions in ventricular dimensions (related to preload) and diastolic pressure (afterload) may be important beneficial effects in some patients. In recent work, angiographic coronary disease progression could be prevented by adequate T_4 replacement in hypothyroidism (220). Thus, THs can protect against arteriosclerosis, presumably due to their metabolic effects on plaque progression. The hypothyroid patient with unstable myocardial ischemia presents a special challenge, particularly when coronary vascular interventions are indicated. Risks of exacerbating myocardial ischemia must be balanced against those of surgery or angioplasty in the hypothyroid state. No increased risk of perioperative death has been observed in hypothyroid patients undergoing coronary revascularization (221). However, higher incidences of intraoperative hypotension and perioperative heart failure were observed. For percutaneous transluminal angioplasty, success rates and risk of complications were comparable in hypo- and euthyroid patients, although there was a trend toward higher risk of hematoma formation in the hypothyroid group (222).

C. Subclinical hypothyroidism

1. Cardiac changes. Subclinical hypothyroidism is common, especially among elderly women (223). There is no clear evidence to date that subclinical hypothyroidism causes clinical heart disease. However, mild thyroid gland failure, evidenced solely by elevation of the serum TSH concentration, may be associated with increased morbidity, particularly for cardiovascular disease, and subtly decreased myocardial contractility (224–228). In subclinical hypothyroidism, impaired LV function and cardiorespiratory adaptation to effort become unmasked during exercise (225). More specifically, these patients have resting LV diastolic dysfunction, evidenced by delayed relaxation, and impaired systolic dysfunction on effort that results in poor exercise capacity (225, 226). These changes are reversible when euthyroidism is restored (229, 230). Flow-mediated vasodilatation, a marker of endothelial function, is significantly impaired in subclinical hypothyroidism (231), and decreased heart rate variability, a marker of autonomic activity, suggests hypofunctional abnormalities in the parasympathetic nervous system (228).

To show association of subclinical hypothyroidism with changes in cardiac parameters, several studies compared selected patients with increased TSH levels and euthyroid controls. Among measures, parameters of LV morphology were shown to be significantly higher in patients with subclinical hypothyroidism compared with controls (228). In contrast, Biondi *et al.* (227) reported no abnormalities of LV morphology seen in the patient group. Doppler-derived indices of diastolic function also were examined by Biondi *et al*. (227) and Monzani *et al*. (228). Clear abnormalities of myocardial relaxation, as indicated by significant prolongation of the isovolumic relaxation time, were established in both studies. However, the significant reduction in the early-to-late diastolic mitral flow velocity ratio (E/A ratio), mostly accounted for by increased A wave of mitral flow velocity (seen in both studies), was reported in the study by Biondi *et al.* (227) but not confirmed in the later study by Monzani *et al.* (228). In terms of systolic function, mean aortic acceleration was demonstrated to be significantly reduced in subclinical hypothyroid patients compared with controls. Moreover, preejection period (PEP) as well as PEP/ejection time ratio were significantly longer in patients than controls. The

ultrasonic video densitometry used provided a morphological characterization of myocardial tissue. The study reported lowering of the cyclic variation index in patients, but not controls, at both the septum and posterior wall. This index was said to be directly related to serum free T_3 level and was inversely related to TSH levels. The changes in this index amplitude suggest early alterations in intramural myocardial function, *i.e.*, impaired intrinsic myocardial contractility, which is in line with the observed inverse relationship between this index and the PEP/ejection time ratio.

L-T_4 therapy was associated with improvement in diastolic dysfunction in each of the studies (207, 208, 227, 228, 232), also indicating reversibility in diastolic dysfunction by L-T_4 therapy. In terms of systolic function, Biondi *et al.* (227) documented improvement from pretreatment values, although no difference when compared with the control group. Likewise, therapy did not induce significant changes in LV morphology. In addition, Monzani *et al.* (228) reported a significant reduction in PEP/ejection time as well as normalization of cyclic variation index. Interestingly, the same PEP/ejection time improvement was also documented in a previous study (229). In this study, the researchers also documented shortening of the interval from Q wave at the ECG to pulse arrival at the brachial artery as well as reduction in cardiac systolic time intervals, with normalization of TSH levels brought about by treatment.

In a study of 10 patients who underwent radionuclide ventriculography before and after achieving euthyroidism by L-T_4 therapy, Forfar *et al.* (226) suggested a subtle impairment of contractile response to exercise in patients with subclinical hypothyroidism which is reversible with L-T_4 treatment. The study demonstrated an improvement in LV ejection fraction (during exercise) with hormonal replacement, which was associated with a steeper slope in the LV pressure-volume relationship at end systole. In addition, a smaller increase in heart rate and an unchanged stroke volume with the enhancement of cardiac output were documented after normal TSH levels were established with L-T_4. Recently, Faber *et al.* (233) looked into the benefit of L-T_4 treatment on hemodynamic regulation in subjects with subclinical hypothyroidism. Results show a 6% reduction in supine mean arterial pressure by oscillometry, 14% increase in upright cardiac output, and 13–20% decrease in systemic vascular resistance. Plasma norepinephrine and epinephrine decreased during L-T_4 treatment as well.

2. Change in lipids and its relation to atherosclerosis. Subclinical hypothyroidism does result in a small increase in LDL cholesterol and a decrease in high-density lipoprotein cholesterol, changes that enhance the risk for development of atherosclerosis and coronary artery disease (234). These changes are based in the marked influence that TH has on lipid metabolism. TH influences lipid metabolism by several mechanisms. For several key enzymes in lipid mechanism, a direct transcriptional effect of T_3 mediated through TRs and binding to TREs has been described. TREs have been identified in the promoter region of the hepatic lipase and the apolipoprotein A1 gene (235, 236). For the LDL receptor genes, TREs have been identified by one group (237), but another group of investigators invoke a different mechanism (238). According to these studies, the sterol-regulatory element binding protein 2, which shows positive transcriptional regulation by TH, mediates the TH-induced increases in the expression of the LDL receptor (238). In the hypothyroid status, LDL receptor mRNA and protein levels are decreased. T_3 also regulates posttranscriptional editing of apolipoprotein mRNA (239). In addition, T_3 is important in hepatic degradation of cholesterol into bile acids by increasing the transcription of the rate-limiting enzyme in the process, the cholesterol 7α-hydroxylase (240, 241). Clinical manifestations of the altered lipid metabolism are especially evident in elderly women. It has been established that subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction (242, 243). Hak *et al.* (244) sampled 1149 women participating in the Rotterdam cross-sectional study and found a higher prevalence of subclinical hypothyroidism in women who had atherosclerosis (odds ratio, 1.7) and a history of myocardial infarction (odds ratio, 2.3) than those who did not have these diseases. Of the study sample that had a heart attack, 14% had subclinical hypothyroidism. Additionally, the association between subclinical hypothyroidism and the prevalence of myocardial infarction and atherosclerosis may be stronger in those individuals who have antibodies to thyroid peroxidase. Furthermore, after coronary revascularization, a trend toward higher rates of chest pain, dissection, and reocclusion has been noted in subjects with subclinical dysfunction (234). Also significantly higher levels of procoagulant Factor VIIC in patients with subclinical hypothyroidism have been observed (242). This increase suggests the presence of a hypercoagulable state, which could increase the risk of atherosclerosis and contribute to the increased prevalence of coronary artery disease in such patients. Finally, smoking contributes to the high incidence of subclinical thyroid failure and aggravates its metabolic effects (245). Subjects with marked TSH elevation and elevated titers of thyroid autoantibodies are at higher risk of unnoticed progression to myxedema. Especially women over 50 yr with TSH levels greater than 10 mU/liter and smoking habits have the highest risk for cardiovascular complications.

The magnitude of the lipid changes and the subtle impairment of LV function and cardiopulmonary exercise capacity, as well as the beneficial hemodynamic changes after L-T_4 therapy in subclinical thyroid dysfunction, justify use of hormone replacement (246, 247). Early L-T_4 treatment reduces the cholesterol level by an average of 8% and normalizes all metabolic effects in smokers; nevertheless, in some patients, L-T_4 therapy may exacerbate angina pectoris or an underlying cardiac arrhythmia. Longitudinal follow-up to define the actual cardiovascular disease risk associated with subclinical hypothyroidism is warranted.

A metaanalysis of 13 studies of patients with subclinical hypothyroidism found that L-T_4 normalized TSH levels during therapy while decreasing total cholesterol serum concentrations by 6–8% (246). In a more recent metaanalysis, Danese *et al.* (243) found slightly smaller reductions in total cholesterol levels (5%). Six of 13 studies observed a reduction in total cholesterol of 5% or less. Pooled analysis also revealed that reductions in total cholesterol were greater in the subclinical hypothyroid group in patients being inade-

quately treated for overt hypothyroidism (17.4 mg/dl average reductions) than the subclinical hypothyroid group.

VI. TH Administration in Patients with Heart Disease

In patients with heart disease, alterations in TH metabolism may contribute to defective myocardial performance (248). Accordingly, THs increase cardiac output by enhancing myocardial contractile performance and decreasing venous compliance (249, 250). In patients with acute myocardial infarction, serum T_3 concentrations fall by about 20%, and serum free T_3 concentrations fall by about 40%, with a nadir on d 4 after the infarction (251, 252). Patients with heart failure also have low serum T_3 concentrations, and the decrease is proportional to the degree of heart failure. In an animal model of heart failure, cardiac deiodinase type III, which degrades T_3 to T_2 was markedly elevated (253). Whether the changes in TH metabolism contribute to the impairment of cardiovascular function in patients with heart failure is not known. In patients with advanced heart failure, a single iv dose of 0.058 mg of T_3 resulted in an increase in cardiac output and a decrease in systemic vascular resistance 2 h after administration, without any evidence of myocardial ischemia, rhythm disturbances, or other untoward effects (254). Favorable results were also obtained with 3, 5-diiodothyropropionic acid, a cardiotonic TH analog given in combination with captopril (255). Furthermore, two placebo-controlled trials (256, 257) showed that administration of 0.1 mg T_4/d improved cardiac and exercise performance in patients with idiopathic dilated cardiomyopathy. The responses of cardiac output and heart rate to dobutamine infusion were also enhanced, probably due to an up-regulation of β1-receptors. Functional capacity markedly improved, together with an increase in peak exercise cardiac output.

Decrease in the serum T_3 concentration that occurs in patients with nonthyroidal illnesses could alter cardiac function and expression of cardiac genes. To address this issue, LV systolic and diastolic function was evaluated in animals in which low serum concentrations of T_3 were induced by caloric restriction (258). Diminished cardiac contractility and altered gene expression similar to those seen in experimental hypothyroidism developed in the animals. Replacement doses of T_3 increased LV function and normalized the expression of T_3-responsive genes, thus providing evidence of the potential therapeutic value of T_3 replacement for the improvement of cardiac contractility in patients with nonthyroidal illnesses. In patients undergoing cardiopulmonary bypass, serum total and free T_3 concentrations also decrease transiently in the immediate postoperative period (259, 260). T_3 administration to correct the decreased T_3 levels has been applied, and improved cardiovascular function has been described (261, 262). Reduction in surgical mortality was suggested by a trial of patients treated with iv T_3 at the time of removal of the aortic cross-clamp, and by another study in which patients at high risk undergoing coronary artery bypass grafting were given T_3 immediately before surgery and for 8 h postoperatively (263). In a randomized study, those given T_3 iv at a dose of 1.4 μg/kg body weight over a period of 6 h (average total dose of T_3, 0.11 mg) had a higher cardiac output and lower systemic vascular resistance during the first 24 h after surgery than those given placebo (264). In this study, the frequency of AF during the first 4 d after surgery was lower in the patients given T_3 (265), although postoperative mortality was not altered. These results were confirmed in a similar trial (266); however, in a third study, in which T_3 or dopamine was compared with placebo, there were no differences in outcome (267). Administration of T_3 had no adverse effects; nevertheless, T_3 administration did not alter most hemodynamic variables studied, the requirement for postoperative adjunctive inotropic agents, or the frequency of the requirement for intraaortic balloon counter pulsation. The frequency of ventricular arrhythmia, hours to extubation, time in the intensive care unit, total hospital stay, or overall mortality were also not altered in the T_3 group compared with the control group.

In children undergoing bypass surgery for the correction of congenital heart disease, serum T_3 concentrations fall by more than 60% and remain low for up to 8 d after surgery (268, 269). Pharmacological evaluation of children given T_3 postoperatively indicated that TH clearance from the circulation was more rapid than predicted from studies of normal adults (270). Randomized studies in infants undergoing cardiopulmonary bypass showed that T_3 repletion could be accomplished safely and with a resulting improvement in postoperative cardiac function (271). In children with congenital heart disease who were given T_3 to restore serum concentrations to normal after surgery, cardiac output increased by more than 20%, and vascular resistance decreased by 25%, as compared with untreated children (272, 273). In summary, although promising, at present, the overall usefulness of acute T_3 administration in the setting of invasive cardiovascular procedures has still not been established.

VII. Cardiovascular and Respiratory Exercise Capacity in Thyroid Disease

An abnormal LV function has been observed in thyrotoxicosis, independent of β-adrenoceptor activation, suggesting a reversible functional cardiomyopathy due to a direct effect on the myocardium of excess in circulating T_3 (274) (Fig. 4). LV ejection fraction was also decreased in patients with myxedema and increased after T_4 therapy (275). Furthermore, thyrotoxicosis has been implicated as a primary cause of decreased cardiorespiratory exercise tolerance (276–278). Anaerobic threshold obtained by respiratory gas analysis on a ramp-loading cycle ergometer is an objective measure of exercise capacity (279). At rest and compared with healthy controls, the majority of cardiorespiratory parameters was similar in patients with untreated thyroid disease. However, during exercise, cardiac indices were significantly changed, and the Doppler parameters were markedly modified, all of which normalized in euthyroidism. Normal LV wall motion was noted during exercise whereas hypothyroid, reduced forced vital capacity and tidal volume at the anaerobic threshold were observed. Also, the increment of minute ventilation and oxygen uptake was significantly lower. Workload and the oxygen uptake per heart beat, a parameter for

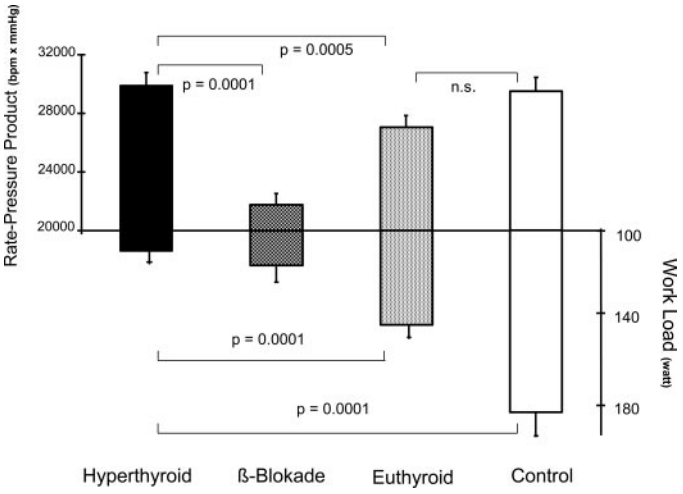

FIG. 4. Rate-pressure product as a parameter of cardiac work (blood pressure × heart rate, *upper panel*) and work load as a parameter of body work (*lower panel*) at maximal exercise (stress two-dimensional echocardiography and cardiorespiratory testing with spiroergometry) in untreated patients with hyperthyroidism, during monotherapy with propranolol (0.16–0.2 g/d), after restoration of euthyroidism, and in age- and sex-matched, healthy control subjects. Data are shown as mean values ± SEM. [Derived from Ref. 276.]

effective cardiorespiratory function, were decreased at the anaerobic threshold and at peak exercise. Cardiorespiratory testing of subjects with thyroid dysfunction revealed ineffective and impaired chronotropic, contractile, and vasodilatory cardiovascular reserves, which were reversible when euthyroidism was restored. Especially in older hyperthyroid patients, marked alterations of cardiopulmonary function were observed. Thus, in thyroid disease, both cardiac structures and function may remain normal at rest; however, impaired LV function and cardiovascular adaptation to effort become unmasked during exercise (280).

VIII. Cardiac Valve Involvement in Autoimmune Thyroid Disease

In patients with thyroid autoimmunity, an increased glycosaminoglycan production is observed in the orbital space, in the pretibial region, and in cardiac valves (281). Glycosaminoglycans are long, unbranched polysaccharide chains composed of repeated disaccharide units. After synthesis in fibroblasts, most of the glycosaminoglycans are released into the extracellular matrix. Being hydrophilic, they attract large amounts of water, thereby forming hydrated gels even at very low concentrations (282–285). The augmented secretion and accumulation of glycosaminoglycans in the cardiac valve lead to thickening of the leaflets. Additional disturbance of collagen synthesis causes prolapse of redundant and thickened (>5 mm) mitral valves into the left atrium. An increased prevalence of myxomatous valves has been reported in thyroid autoimmunity (286, 287). At our institution, the prevalence of myxomatous valves was investigated in patients with Graves' disease, Hashimoto's thyroiditis, toxic nodular goiter, and controls. Myxomatous mitral valve was present in 36 and 33% of the patients with immunthyroiditis and Graves' disease, respectively, but in none of the toxic nodular goiter group (288, 289). In patients with thyroiditis, mitral regurgitation was observed in 28%, whereas myxomatous aortic and tricuspid valves were seen in 22 and 6%, respectively. Thyroid function did not influence the incidence and intensity of the myxomatous valve degeneration, and the valve prolapse was not attributable to myocardial dysfunction caused by a direct effect of THs. A potential link between autoimmune thyroid disease and myxomatous valves is suggested by histochemical studies of tissues affected directly in these disorders (290). A pathological characteristic of the myxomatous valves is a significant increase in the amount of glycosamonoglycans normally found in the superficial zone of connective tissue on the ventricular surface of the floppy mitral valve cusp. Mucinous changes extending into the elongated "chordae tendinae," further increasing the redundancy required for interchordal hooding or prolapse, have been seen. Given the rare but possible cardiac (mitral regurgitation, endocarditis, thromboembolism, arrhythmic sudden death) and neurological (cerebral embolic event) complications (152, 291–293), physicians may look for myxomatous involvement of the cardiac valves in patients with thyroid autoimmunity. Especially in those with a heart murmur, an echocardiogram may be justified, and if a myxomatous valve is present, prophylactic antibiotic treatment would be recommended when appropriate.

IX. Summary and Perspectives

TH have profound effects on the heart and circulation. Measures of LV contractility have demonstrated supranormal systolic and diastolic function. These changes arise from alterations in systemic hemodynamic and T_3-mediated effects on cardiac myocyte-specific gene expression. T_3 effects such as the enhanced velocity of cardiac contraction and the increased speed of diastolic relaxation can be traced to T_3-induced changes in the level of specific mRNAs and proteins like MHCα and -β or the Ca^{++}ATPase of the sarcoplasmic reticulum. Release of Ca^{++} and its reuptake into the sarcoplasmic reticulum are critical determinants of systolic contractile function and diastolic relaxation. Thus, changes in the relative amounts of these proteins and the state of phosphorylation of phospholamban may account for altered diastolic function in both heart failure and thyroid disease. TH also regulates several plasma-membrane ion transporters at both the transcriptional and posttranscriptional levels, thus coordinating the electrochemical and mechanical responses of the myocardium. Other T_3-induced changes result from increased sensitivity of the sympathetic system, and some T_3 effects may be mediated by an increased demand on the periphery. TH has also extranuclear actions in cardiac myocytes. In the short term, T_3 changes the performance characteristics of various sodium, potassium, and calcium channels in the heart, and changes in intracellular levels of calcium and potassium can increase inotropy and chronotropy.

Cardiovascular signs of hyperthyroidism include tachycardia, widened pulse pressure, marked increases in cardiac output, and impaired cardiovascular and respiratory exercise capacity. In the elderly hyperthyroid patient, symptoms and signs of heart failure and/or worsening of angina pectoris may dominate the clinical picture and mask the more

classical endocrine manifestations of the disease. Long-term follow-up studies have revealed increased mortality in those with a past history of overt hyperthyroidism, as well as those with subclinical hyperthyroidism. Supraventricular arrhythmias, particularly AF, in older patients may account for some of the excess cardio- and cerebrovascular mortality described, especially because AF is known to predispose to embolic phenomena. Regarding the high incidence of AF in older patients with hyperthyroidism, it is also important to detect subclinical hyperthyroidism, thus warranting the measurement of the serum TSH concentration for an early recognition and treatment. Most cardiac abnormalities return to normal once a euthyroid state has been achieved, although AF may persist in a minority. Optimal treatment requires rapid and definitive antithyroid therapy. Furthermore, anticoagulation is recommended for hyperthyroid patients older than 50 yr with AF and those who have histories of previous emboli, hypertension, or with left atrial enlargement and/or myxomatous cardiac valves.

In summary, the molecular basis of TH action in the heart continues to be explored. Identification of specific T_3-responsive ion channels will provide further information related to molecular mechanism by which changes in thyroid status alter heart rate and electrical conductivity. The diminished contractile activity of the hypothyroid heart resembles findings in heart failure and may warrant further exploration of therapeutic approaches using TH or its analogs to improve cardiac function in heart failure. The availability of mouse models with deletion of specific T_3 receptor isoforms will aid in gaining additional knowledge about the molecular mechanisms that mediate T_3 action in the heart.

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