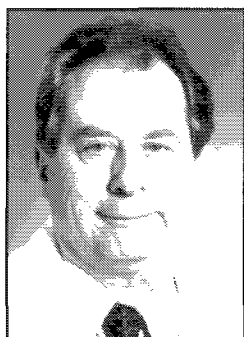


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Editor's Summary: *Cardiovascular abnormalities have always been recognized as a hallmark of thyroid dysfunction. In this review, the author summarizes recent advances in the molecular basis of thyroid hormone action on the heart and applies these new findings to help us understand the clinical observations. Dr Dillmann reviews the effect of thyroid hormone on the genes involved in controlling heart rate, contractility, and the sympathetic nervous system. Studies in knockout animals are also reviewed and used to explain the role of specific thyroid hormone receptor subtypes on the heart. Last, the author provides some clinical guidelines for therapy of the cardiovascular effects of thyroid dysfunction.*

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Thyroid Hormone Influences on the Cardiovascular System: Molecular and Clinical Studies

The important role that thyroid hormones play in modifying cardiovascular function has been appreciated for a long time.^{1,2} The principles governing the interactions between thyroid hormone and the cardiovascular system were reviewed several years ago in *Thyroid Today* in 1996 (Vol. XXI, 1) and in other publications.^{3,4} Since then, interesting new information has accumulated that warrants a timely review of this topic. For example, recent studies in mice with null mutations of the thyroid hormone α -receptor ($TR\alpha$) indicate that a decreased heart rate occurs in such animals and that contractile function is also diminished.^{5,6} In contrast, mice with deletion of thyroid hormone β -receptor ($TR\beta$) show no impairment in contractile or electrophysiologic action of the heart.⁶ In addition, novel thyroid hormone analogs with preferred binding to $TR\beta$ have been described. One of these $TR\beta$ -preferred analogs, GC-1,⁷ shows a marked differential effect by lowering lipid levels without significantly increasing heart rate in hypothyroid animal models.⁸ Recent clinical studies also show that in patients with heart failure, the level of thyroid hormone receptors is significantly decreased, an alteration that may contribute to the heart

failure itself.⁹ With this and other recent findings in mind, I will point out specific routes by which triiodothyronine (T_3) may influence cardiovascular function. The mechanisms of T_3 action are briefly summarized. In addition, possible T_3 target genes in the heart will be discussed. Last, clinical aspects of hyperthyroid and hypothyroid heart disease are considered. I will use the term " T_3 action" in this review because most of the biologic actions of thyroxine (T_4) are mediated by its conversion to T_3 .

**Routes by Which
 T_3 Influences
Cardiovascular Function**

More vigorous cardiac contraction caused by T_3 is largely mediated by direct actions of T_3 in the cells of the heart. Other mechanisms, however, especially an increase in hemodynamic load and potentially an increased sensitivity of the β -sympathetic system, also contribute to T_3 -mediated changes in cardiac contractile function. The direct T_3 effect on the heart occurs primarily in cardiac myocytes, which represent one third of the cells of the heart but, due to their large size, contain two thirds of the cardiac protein. In contrast, cardiac fibroblasts represent two thirds of the cardiac cells but are much smaller than other cardiac cells. The number of T_3 receptors (TRs) in cardiac fibroblasts is only about 10% of the number of TRs in cardiac myocytes. In addition, the vascular system of the heart contributes a small number of cardiac cells, including endothelial cells, vascular smooth muscle cells, and a few

interstitial lymphocytes. Of interest is that in cardiac myocytes of the rodent heart, there is no significant conversion of T_4 to T_3 . Recently, transgenic mice have been produced in which a cardiac myocyte-specific promoter derived from the myosin heavy-chain alpha (MHC α) gene directed expression of deiodinase type II in mouse heart myocytes.¹⁰ This procedure increases the local conversion of T_4 to T_3 , thus leading to increased myocardial T_3 levels. These mice developed a mild hyperthyroidlike phenotype, in the presence of normal serum thyroid hormone levels. The effects of T_3 on the heart result predominantly from the interaction of T_3 with specific TRs. This interaction will be discussed in more detail below. Some reports have demonstrated rapid T_3 effects, for example, on ion transport in isolated cardiac myocytes.¹¹ These, however, are most likely not primarily mediated by TRs.

T_3 Receptor-Based Mechanism of T_3 Action. Thyroid hormone action is largely mediated by the high-affinity binding of T_3 to nuclear TRs, which are members of the nuclear receptor superfamily. The TR-based mechanism of T_3 action has recently been reviewed,¹² and only a brief summary will be given here. TR resides in a chromatin-bound form in the nucleus, binding to T_3 response elements (TREs) of T_3 -responsive genes. Two separate genes have been identified that encode TRs, designated TR α and TR β . These are located on different chromosomes. Different splice variants arise from these genes. From the TR α gene are derived the T_3 -binding isoform TR α 1 and the nonbinding- T_3 isoforms TR α 2 and TR α 3. TR α 2 acts as a weak

dominant negative transcription factor.¹³ From the TR β gene arises TR β 1, which is ubiquitously distributed, and TR β 2, which is expressed at high levels in the pituitary. Recently, a TR β 3 isoform has also been described.¹⁴ TR β 3 occurs at very low levels in the heart. TR unoccupied by T_3 represses basal transcription and markedly diminishes expression of the target gene. T_3 -occupied TR increases transcription of a significant number of target genes by binding to TREs of various configurations. Most TREs contain consensus sequences composed of a hexameric half site with the AGGTCA consensus motif. Those half sites can be arranged as 2 half sites with the same orientation spaced by 4 base pairs and are termed *direct repeat plus 4* or DR4 elements. Other arrangements include a palindromic or an inverted palindromic half-site arrangement. T_3 -mediated transcriptional activity of TR occurs by recruitment of coactivator proteins that bind to a specific region in the C-terminal area of TR.¹² In addition, they mediate increased histone acetylation, which results in a loosening of chromatin structure and promotes transcriptional activation. The importance of coactivators like SRC-1 in T_3 action is demonstrated by the finding that mice that lack SRC-1 are T_3 resistant.¹⁵ In contrast, TR that is not occupied by T_3 associates with corepressors like the silencing mediator for retinoid and thyroid hormone (SMRT) or another corepressor termed *N-COR*.¹² These corepressors, along with other factors, form a multiprotein complex that includes histone deacetylases. The deacetylases repress transcription because

they decrease acetylation of histones, causing a more compact chromatin structure and thereby excluding interactions with the basal transcriptional machinery.

Rapid T₃ Effects Mediated by Nongenomic Mechanisms. Nongenomic effects of thyroid hormone occur rapidly, within 0.5 to 2 hours, and do not require protein synthesis. The primary event in their mediation does not involve T₃ binding to TR. Examples of such effects have been demonstrated when isolated cardiac myocytes are exposed to T₃. This T₃ exposure results in a rapid recruitment, within 4 minutes, of slow inactivating sodium channels in cardiac myocytes.¹¹ Similarly, a direct nuclear receptor-independent effect of thyroid hormone on the calcium ATPase of the sarcolemma has been demonstrated in reconstituted cardiac membranes.¹⁶ In these experiments, T₃ stimulated the calcium ATPase and calcium movement across the cell membrane. Examples of an interaction between TR-dependent and TR-independent effects have also been reported. For example, T₄ nongenomically increases serine phosphorylation of TR.¹⁷ It should, however, also be noted that thyroid hormones are highly lipophilic, and it is conceivable that thyroid hormone is concentrated in the phospholipid bilayer of the cardiac myocyte membrane. In addition, as discussed below, mice with a null mutation of both TR α and TR β have very high thyroid hormone levels but exhibit a hypothyroid phenotype, with a decreased heart rate and decreased body temperature. If extranuclear effects of thyroid hormone significantly contribute

to the physiologic action of thyroid hormone, the observed phenotype would not have been expected in the mice lacking TRs. Nevertheless, the findings in these mice do not exclude a more subtle contribution to thyroid hormone action by nongenomic effects.

Interactions Between T₃ and the Sympathetic System

Patients with hyperthyroidism and patients with excess catecholamine production (as occurs with pheochromocytomas) share many symptoms, such as tachycardia, a hypermetabolic state, weight loss, and increased sweating. In addition, β -sympathetic blockade has beneficial effects in hyperthyroid patients. These clinical observations suggest that increased sympathetic action occurs with hyperthyroidism. Furthermore, various components of the β -adrenergic signaling systems are increased in the hyperthyroid state, including increases in β -adrenergic receptors, in components of the guanine nucleotide regulatory system, and in adenylyl cyclase isoforms V and VI. In spite of these changes, the overall sensitivity of the β -adrenergic system in hyperthyroid animals appears to be normal or only marginally increased.^{18,19} The predominance of direct T₃ effects on the heart, independent of the β -adrenergic system, is also demonstrated in studies of hyperthyroid dogs, which show that in spite of complete sympathetic blockade, certain cardiac parameters remain increased.²⁰ Therefore, the sympathetic system does not play an essential role in mediating the

cardiovascular symptoms of hyperthyroidism.

Mediated Hemodynamic Changes of T₃

T₃-induced increases in cardiac contraction are modified by hemodynamic changes that accompany the hyperthyroid state. An increased hemodynamic load on the heart occurs in hyperthyroidism as a result of an increased return of blood to the heart and an increase in blood volume.²¹ Hyperthyroidism induces a decrease in arterial tone and an increase in venous tone that promotes flow of blood back to the right heart.²² The increase in blood volume is triggered initially by a decrease in vascular resistance, which then leads to diminished vascular filling. This, in turn, activates the renin-angiotensin-aldosterone axis. Increased aldosterone levels promote renal sodium resorption and an increase in plasma volume. That these hemodynamic effects are not primary determinants of the increase in cardiac contractile status in hyperthyroidism is indicated by the following findings. Isolated perfused hearts obtained from hyperthyroid animals, which are removed from any hemodynamic effects, also show marked increases in cardiac contraction. Furthermore, exposing isolated cardiac myocytes to T₃ leads to increases in protein synthesis and increased expression of specific genes that are directly linked to an increased contractile state.²³ The T₃ effects on the cardiovascular system are summarized in Table 1.

■ Table 1

T₃ Effects on the Cardiovascular System

Mediation of T ₃ Effects	Consequences of T ₃ Effects	
Direct cardiac effects	Cardiac hypertrophy	
T ₃ -receptor mediated	Myocyte ↑	Increase in total and specific cardiac proteins
Nongenomic	Nonmyocyte	Decrease in collagen
Peripheral hemodynamic effects	Contractility	
Arterial dilatation	Inotropic ↑	Speed and force of systolic contraction ↑
Venous constriction		
Increased blood volume	Lusitropic ↑	Speed of diastolic relaxation ↑
Adrenergic system effects	Electrical activity	
β-Adrenergic receptor ↑	Chronotropic ↑	Ability to generate electrical impulse → rate ↑
Gs ↑		
Adenylate cyclase V,VI ↑	Dromotropic ↑	Ability to conduct electrical impulse → speed of conduction ↑

Contractile and Electrical Actions of T₃

T₃ increases the force and speed of systolic contraction (inotropic effect), accelerates diastolic relaxation (lusitropic effect), and increases heart rate (chronotropic effect). The detailed mechanisms by which these profound effects of T₃ on cardiac function are mediated have recently been further clarified.

Contractile Activity. The speed and force of cardiac contraction are largely determined by the number of cross-bridges formed between the globular head of myosin in the thick filament and its interaction with actin molecules, forming a beadlike chain of polymers in the thin filament. For the myosin globular head to be able to interact with the actin filament, the inhibitory protein troponin I needs to move from the position it

assumes during cardiac relaxation, which prevents this interaction. Calcium binding to troponin C triggers this movement. In addition, calcium binding to myosin increases myosin ATPase activity by regulating the myosin attachment–detachment cycle.²⁴ Thus, the 2 crucial contributors to systolic force and speed generation are the systolic calcium level in the cytosol and the myosin ATPase activity. Both of these 2 crucial contributors to cardiac function are influenced by T₃. There are several different myosin isoforms that contain a specific pattern of myosin heavy-chain proteins. Each heavy-chain protein is encoded on a separate gene. Myosin V1, which makes up about 70% of total myosin in the rodent heart and contains MHCα, has a high myosin ATPase activity. In contrast, myosin V3, containing myosin heavy-chain beta (MHCβ), has a much lower myosin ATPase activity. In the MHCα gene, a

strong TRE occurs, which markedly increases transcription of this gene when T₃ is bound to the TR.²⁵

In contrast, MHCβ has a negative TRE, and expression of the MHCβ is suppressed by T₃-bound TR. It should be mentioned that in the human heart, MHCβ and myosin V3 predominate and only a small fraction of MHCα and myosin V1 (5%-10%) is present.²⁶ T₃-induced changes in MHC isoform gene expression contribute appropriately only a modest amount to the hyperthyroid cardiac phenotype. A crucial contribution to contractile action is made, however, by changes in systolic calcium levels. Calcium enters the cardiac myocyte through the L-type calcium channel, and a small amount of triggering calcium induces the release of a larger amount of calcium out of the sarcoplasmic reticulum (SR) through the calcium channel of the SR termed the *ryanodine channel*.²⁷ This channel was initially identified by its binding to a plant-derived toxic compound, ryanodine. T₃ both increases influx of calcium through the L-type calcium channel and enhances egress of calcium out of the SR through the ryanodine channel. The mRNAs coding for these genes are T₃ responsive. Other cardiac genes that are influenced by T₃ and participate in contractile function are summarized in Table 2.

The main mediator for the termination of cardiac contractile action and the initiation of cardiac relaxation during diastole is the lowering of calcium in the cytosol of the cardiac myocyte. A pump localized in the SR surrounding myofibrils transports calcium from the cytosol into the SR. The Ca²⁺ ATPase of the sarcoplasmic reticulum (SERCA2) consumes ATP in

■ Table 2a					
T₃ Effects in the Heart					
Myocytes—Sarcoplasmic Reticulum					
Gene	Transcription	TRE	mRNA	Protein	Activity
SERCA2	↑	Yes	↑↑↑	↑↑↑	Ca ²⁺ sequestration Diastolic relaxation ↑
Phospholamban	N/D	N/D	↓T ₃ ↓Tx	N/D	SERCA2 inhibition Diastolic relaxation ↓
Ryanodine channel (Ca ²⁺ channel)	N/D	N/D	↑↑↑	N/D	Ca ²⁺ efflux ↑ Systolic contraction ↑

■ Table 2b					
Myocytes—Myofibrils					
Gene	Transcription	TRE	mRNA	Protein	Activity
MHC α	↑	Yes	↑↑↑	↑↑↑	Speed of contraction ↑
MHC β	↓	Yes	↓↓↓	↓↓↓	Speed of 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 contractile protein

■ Table 2c					
Myocytes—Sarcolemma					
Gene	Transcription	TRE	mRNA	Protein	Activity
NaK ATPase			↑Tx→E	↑Tx→E	Na ⁺ efflux ↑
α_1			↑Tx→E	↑Tx→E	
α_2			↑Tx→E	↑Tx→E	
β					
Ca ²⁺ ATPase	N/D	N/D	N/D	N/D	Ca ²⁺ efflux ↑ (EN)
β_1 receptor	↑	N/D	↑↑	↑↑	Adrenergic ↑
G _i α	N/D	N/D	↓↓	↓↓	Adrenergic ↓
G _i β	N/D	N/D	↓↓	↓↓	Adrenergic ↓
Gs	N/D	N/D	N/D	↑	Adrenergic ↑
Adenylate cyclase V,VI	N/D	N/D	N/D	↑	Adrenergic ↑

↑ indicates an increase of parameter after thyroid hormone administration.
↓ indicates a decrease in the hypothyroid state.
N/D, not determined.
EN, extranuclear effect.
For phases of action potential see Figure 1.

■ Table 2d

**T₃ Effects in the Heart
Myocytes—Ion Channels**

Gene	Transcription	TRE	mRNA	Protein	Activity (A)	Function
Na ⁺ channel	N/D	N/D	N/D	N/D	↑ (EN)	Phase 0, Na ⁺ influx Depolarization
Kv4.2	N/D	N/D	↑	N/D	↑	Phase 1, I _{to} transient outward rectifier
L-type calcium channel	N/D	N/D	↑	N/D	↑	Phase 2, Ca ²⁺ influx trigger for SR Ca ²⁺ release
Kv1.5	N/D	N/D	↑	N/D	↑	Phase 3 delayed rectifier
minK	N/D	N/D	↓	N/D	↑	Phase 3 forms I _{Ks} with KvLqT
I _{K1}	N/D	N/D	N/D	N/D	↑ (EN)	Phases 3, 4, inward rectifier
HCN2	N/D	N/D	↑	N/D	↑	Phase 4, pacemaker role
HCN4	N/D	N/D	↑	N/D	↑	Phase 4, pacemaker role

this process. In the promoter of the SERCA gene, several TREs occur and T₃ markedly increases SERCA2 transcription.²³ When transgenic mice expressing the SERCA2 gene are made hypothyroid, the expected delayed diastolic relaxation occurring with hypothyroidism is markedly accelerated.²⁸ This finding highlights the importance of the SERCA2 gene in mediating T₃-induced increases in diastolic relaxation. SERCA2 activity is also regulated by phospholamban, a small protein that inhibits the pump activity until this protein is phosphorylated. T₃ lowers phospholamban mRNA levels. It has been shown that mice with a knockout of the phospholamban gene have a very high cardiac contractile state, a state that may be close to the maximum level. Administration of T₃ to such mice does not further increase cardiac contraction.²⁹

Table 2 lists additional proteins that are T₃ responsive and contribute to changes in diastolic relaxation.

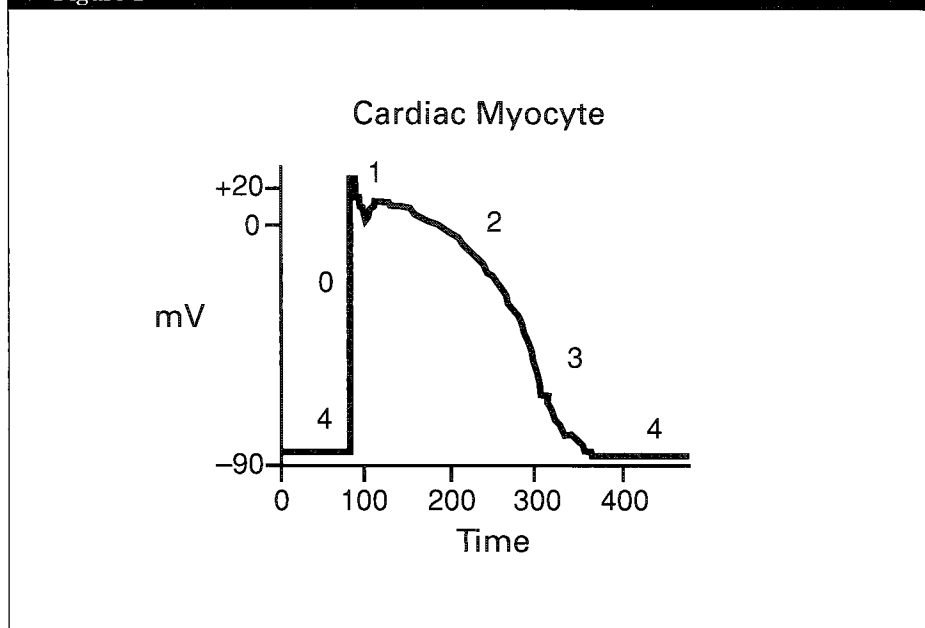
Influences of T₃ on Electrical Activity. Tachycardia and an increased propensity for atrial fibrillation are hallmarks of hyperthyroidism. Heart rate is generated in specialized myocytes of the sinus node located in the right atrium. Several ion currents contribute to this complex process³⁰ (Figure 1), and the genes coding for these ion currents are now being identified. The action potential of a new cardiac beat is generated when the end diastolic potential of about -80 mV becomes quickly depolarized, developing to a positive potential of +20 mV. This is accomplished by the inflow of positive sodium ions into ventricular myocytes. In the specialized myocytes of the sinus node, the depolarizing current is

transmitted by calcium (rather than sodium) entering through L-type calcium channels. A complex mix of ion channels mediates the subsequent repolarization of the action potential. In phases 2, 3, and 4 of the action potential, voltage-gated potassium channels³¹ and hyperpolarization-activated currents like the I_f current make essential contributions. The I_f current carries both sodium and potassium and is encoded by 2 separate genes, HCN4 and HCN2. Both the HCN2 and HCN4 genes are markedly thyroid hormone responsive at the level of gene expression.^{6,32} Increased T₃-mediated activation of the I_f current probably contributes in an important way to T₃ influences on heart rate. T₃ effects on other ion currents and the genes that code for them are summarized in Table 2 and Figure 1.

The Beat Goes on, TR or no TR

Since 1996, several mouse lines have been generated in which either some or all isoforms of TR have been deleted. TR α , TR α 1, TR β , and TR α plus TR β null mutant mice have been generated.³³⁻³⁷ Such mice are termed *TR null mutants* or *knockout (KO) mice*. A significant cardiac phenotype characterized by decreased heart rate occurs in mice that have deletion of TR α .^{6,35} The different types of TR α KO mice include those constructed by B. Vennstrom's laboratory in which a TR α splice mutant was engineered, allowing for the expression of TR α 2 but eliminating the expression of the T₃-binding isoform TR α 1.³⁵ In other mice, generated by J. Samarut's group, the DNA-binding region of TR α encoded by exon 2 was deleted.³⁴ These latter mice, termed *TR*^{-/-}, have a decrease in body size, hypothermia, and a limited life span and do not reproduce. These mice were found, however, to have partial TR α transcripts present. Therefore, J. Samarut's laboratory also constructed a TR α KO mouse line in which exons 5, 6, and 7 of the TR α gene were deleted,³⁷ eliminating expression of the short partial TR transcripts. These mice have a normal body size and life span and reproduce; they have been termed *TR*^{0/0} mice. Most important, all 3 types of TR α KO mice have bradycardia. In *TR*^{0/0} and *TR*^{-/-}, the mRNA coding for specific cardiac ion channels was quantitated and both HCN2 and HCN4 mRNA was diminished in the cardiac ventricle and atrium.⁶ In addition, mRNA for

■ Figure 1



Activity of ion channels. The cardiac myocyte action potential consists of 5 phases. Ion currents influenced by the thyroid status are summarized in Table 2d and are only briefly mentioned here. Many other currents also contribute to the different action potential phases. Phase zero is the depolarization phase and is carried by Na⁺ influx through the I_{Na} current in the contractile myocytes. In the myocytes of the SA node, where pacemaking action occurs, Ca²⁺ influx through L-type Ca²⁺ channels provides for rapid depolarization. During phase 1, the early repolarization phase, the I_{t0} current encoded by the Kv2.4 gene is active. During phase 2, the plateau phase, L-type Ca²⁺ channels are activated and provide the Ca²⁺ trigger for further calcium release from the SR. Phase 3 provides for further repolarization by delayed rectifier channels. Some inward rectifier channels (I_{K1}) are also activated during phase 3. During phase 4, the I_f channel is activated and contributes to the generation of the next heartbeat. This occurs during phase zero, with opening of Ca²⁺ channels in the SA node and Na⁺ channels in contractile myocytes.

Kv4.2 was decreased and minK mRNA was increased.⁶ Kv4.2 constitutes the I_{t0} channel, which is activated during the second phase of the cardiac action potential. The minK protein participates in phase 3 of the cardiac action potential.³¹ Wild-type mice that are made hypothyroid show similar quantitative changes in the mRNA coding for these ion channels.⁶ T₃ also influences expression of Kv1.5 mRNA.³⁸ In addition to the diminished heart rate, the *TR*^{0/0} mice showed a markedly diminished contractile phenotype. Corresponding to the diminished contractile phenotype, the mRNAs for MHC α and SERCA2 were

significantly diminished, whereas MHC β mRNA was increased.⁶

In contrast to the marked electrophysiologic and contractile changes of TR α KO mice, no significant electrophysiologic or contractile phenotype was observed in TR β KO mice.⁶ The TR β KO mice show some evidence of hyperthyroidism because of the loss of the inhibitory effect of T₃-occupied TR β 2 on thyroid-stimulating hormone (TSH) gene expression. Consequently, plasma thyroid hormone levels are elevated. The TR β KO mice have a rapid heart rate, consistent with the hyperthyroid status. When the mice are made euthyroid, they have a normal

heart rate and contractile function under basal conditions. In spite of the electrophysiologic and contractile function of these mice, TR β does make some contributions to cardiac action, as indicated by the following findings. In TR α KO mice, where TR β is left as the only functional TR, T₃ administration increases heart rate from a decreased level.⁵ Although the heart rate is not normalized by T₃, it is significantly increased, indicating that TR β mediates this increase. Additional evidence for the role of TR β in the heart comes from mice in which the exon coding for the PV mutant of TR β is exchanged for the wild-type exon.³⁹ This mutant is identical to that of patients with thyroid hormone resistance. In the PV mutant mice, the TR β mutant isoform is driven by the normal TR β promoter, resulting in mutant TR β expression in tissues where wild-type TR β is normally expressed. These mice have marked bradycardia (unpublished observation). Recently, mice with null mutations for both TR α and TR β have been generated. These mice are viable and have very high T₃ levels, but exhibit bradycardia and hypothermia.^{36,40} The phenotypes of TR α KO, TR β KO, and TR α KO plus TR β KO mice are still being actively characterized, and additional insights into T₃ effects on cardiovascular symptoms will be gained from these models.

Clinical Aspects of T₃-Induced Changes in Cardiovascular Function

Hyperthyroidism. Cardiovascular signs and symptoms are complaints that frequently bring

the hyperthyroid patient to initial medical attention. These include palpitation manifested by a vigorous and irregular heartbeat, a widened pulse pressure, and shortness of breath on exertion. These symptoms may be even more pronounced in older patients. Further, symptoms of angina pectoris can first present during hyperthyroid episodes, especially in the older age group. The occurrence of angina pectoris has even been described in the presence of normal coronary arteries and may reflect vascular spasm.⁴¹ In patients with significant tachycardia, the cardiac symptoms can progress to heart failure,⁴² a form of rapid heart rate-induced cardiac failure. On physical examination, the first heart sound is frequently increased and an accentuated pulmonic component of the second heart sound can be noticed. Systolic murmurs indicating mitral and tricuspid valve regurgitation are noted in hyperthyroid patients. These murmurs result most likely from papillary muscle dysfunction and disappear when a euthyroid state is reestablished. Patients with autoimmune-based hyperthyroidism, such as Graves' disease, show an increased production of glycosaminoglycan (GAG), which also involves the cardiac valve⁴³ in addition to the orbital space and the pretibial region. The increased GAG accumulation leads to thickening of the cardiac valves, which results in mitral valve prolapse. The hyperdynamic state accompanying hyperthyroidism, however, further promotes the manifestations resulting from the mitral valve

prolapse.⁴⁴ A systolic scratching sound, the so-called Means-Lerman Scratch, can also be audible in the left second intercostal space. The rubbing of pleural and pericardial surfaces against each other due to the hyperdynamic action of the heart most likely creates this sound. Over the thyroid area, a venous hum may be audible; it results from the marked increase in blood supply to the hypertrophied thyroid gland. Blood pressure measurements frequently reveal an increased systolic level, which leads to a widened pulse pressure with a normal diastolic pressure. Diastolic hypertension, however, is not linked to the hyperthyroid state but occurs with hypothyroidism, as discussed below. At least half of the patients with hyperthyroidism exhibit sinus tachycardia with 100 beats per minute or more.⁴⁵ In approximately 10% to 15% of patients with marked hyperthyroidism, atrial fibrillation occurs. In patients with apathetic hyperthyroidism, that is, not showing other outright manifestations of hyperthyroidism, increased thyroid hormone levels as an underlying cause for the atrial fibrillation can frequently be overlooked. In elderly patients with atrial fibrillation, a serum TSH level should be determined to diagnose hyperthyroidism in a timely manner. Ventricular arrhythmias, which are often of a more serious nature than atrial arrhythmias, occur at a higher incidence in patients with toxic goiter, whereas in patients with Graves' disease, this arrhythmia is not significantly increased.⁴⁵

Heart rate disturbances, especially tachycardia and atrial fibrillation, can occur in patients with subclinical hyperthyroidism, as defined by depressed TSH levels with normal T_4 and T_3 levels.⁴⁶ In addition, subclinical hyperthyroidism can lead to an increase in left ventricular mass and left ventricular contractile function.⁴⁷ A setting of subclinical hyperthyroidism with cardiac symptoms occurs especially frequently in patients who are on T_4 replacement therapy, which can lead to suppressed TSH levels.

In patients treated with amiodarone, which is an iodine-rich antiarrhythmic compound, hyperthyroidism can develop and is frequently initially overlooked. The patient's arrhythmia may get worse, resulting in a further dose increase of amiodarone because the physician may not recognize that the underlying cause for the worsening arrhythmia is a progressive state of hyperthyroidism. Two different types of amiodarone-induced hyperthyroidism occur, one resulting from the increased iodine exposure and increased thyroid hormone production, termed *type I thyrotoxicosis*. In addition, a destructive thyrotoxicosis (type II) occurs with a thyroiditis, leading to a firm thyroid gland and to increased release of thyroid hormone.⁴⁸ The type II thyrotoxicosis involves inflammatory processes, and inflammatory cytokines like interleukin-6 are increased in this group of patients.⁴⁸

Treatment of Cardiac Symptoms in Thyrotoxic Patients. The central treatment objective in hyperthyroid patients

with cardiovascular symptoms is to return them to a euthyroid status as soon as possible. Antithyroid drug treatment is the preferred mode of thyroid hormone therapy for most of these patients. Other options include treatment with radioactive iodine or surgical thyroidectomy. The former can take several weeks until it becomes fully effective; the latter provides a rapid method of returning the patient to a euthyroid status. However, most clinicians are reluctant to subject patients with cardiac toxicity to a surgical procedure. In addition, a euthyroid status should be achieved before thyroid surgery is performed.

In patients with a rapid heart rate or atrial arrhythmias, sympathetic blockade can markedly ameliorate these symptoms. Furthermore, some β -sympathetic blocking agents like propranolol also modestly inhibit T_4 to T_3 conversion. Pulmonary diseases like asthma or chronic obstructive lung disease, however, are relative contraindications to the use of a β -adrenergic antagonist. In addition, propranolol by itself has a negative contractile effect, and if the hyperthyroid patient does not have rapid heart rate-induced heart failure, treatment with propranolol could lead to a further worsening of the underlying heart failure. In patients exhibiting underlying heart failure, digitalis treatment may be considered, but digitalis toxicity can develop in hyperthyroid patients at doses that are generally well tolerated in the euthyroid patient population. Administration of calcium channel blockers also leads to the slowing of the heart rate in patients with

thyrotoxicosis; however, these compounds also lead to peripheral vascular dilatation, which is already increased in hyperthyroid patients. Calcium channel blockers may therefore have unfavorable hemodynamic effects that lead to further decompensation. Hyperthyroid patients who show signs of heart failure, including significant pulmonary or peripheral edema, can be treated with diuretics, like furosemide.

The use of anticoagulation therapy in patients with atrial fibrillation is controversial. Especially in younger patients with hypertension and atrial fibrillation with no evidence of underlying heart disease or thrombus formation in the atrium, the risk of anticoagulation therapy can outweigh its benefits.⁴⁹ Older patients, however, who more frequently have underlying heart disease and an increased propensity for embolic complications, should be anticoagulated.

The treatment of hyperthyroidism induced by the antiarrhythmic agent amiodarone can present significant difficulties. Distinguishing between iodine-induced type I thyrotoxicosis versus type II destructive thyrotoxicosis is important. For type I thyrotoxicosis, antithyroid medication and potassium perchlorate at doses of 250 mg 3 times a day can be used.⁴⁸ Potassium perchlorate will lead to iodine depletion of the thyroid gland. For the type II form, antithyroid medication and high doses of a glucocorticoid, such as 60 mg of prednisone, are frequently beneficial. Some patients are very treatment resistant to this medical therapy and ultimately require a thyroidectomy.

Hypothyroidism. In contrast to hyperthyroidism-induced cardiac manifestations, such as tachycardia and atrial fibrillation, which occur early in the course of hyperthyroidism, the cardiac manifestations of hypothyroidism are slow to develop. Hypothyroidism of significant duration and severity leads to decreased exercise tolerance, dyspnea on exertion, and easy fatigability. Bradycardia occurs commonly in patients with hypothyroidism, but it is not uniformly present. On physical examination, in addition to bradycardia, one may find an elevated blood pressure. The incidence of true hypertension, which manifests itself as an elevated diastolic and systolic blood pressure, is approximately 10% to 20% in patients with hypothyroidism.⁵⁰ Heart sounds are frequently difficult to hear and are faint and distant. There may be an increased cardiac silhouette apparent on chest x-ray. The increased cardiac silhouette frequently results from a pericardial effusion, which rarely leads to cardiac tamponade. In patients with severe long-standing hypothyroidism, a nonpitting edema due to mucopolysaccharide accumulation develops. This nonpitting edema may be superimposed on the pitting edema secondary to congestive heart failure.

A decreased cardiac output is often balanced by a decreased peripheral oxygen demand. In hypothyroid patients, however, congestive heart failure can develop if an additional stress, such as hypertension or an ischemic event, is placed on the heart. Impairment in contractile function of the hypothyroid heart results primarily from slow

diastolic relaxation that requires an increase in filling pressure to provide for normal cardiac filling during diastole. In addition, contraction velocity is slowed during systole and the heart has to contract against increased resistance in the periphery due to the elevated blood pressure.

The distinction between hemodynamic changes as a consequence of hypothyroidism versus the occurrence of congestive heart failure can sometimes be difficult to make. The following are some distinguishing signs:

1. Patients with congestive heart failure have a diminished cardiac response to exercise versus a normal exercise response in hypothyroid patients.

2. The cardiac contractile response to therapeutic maneuvers can be used to distinguish the 2 entities. For example, the hypothyroidism-induced alterations in cardiac contractility respond well to thyroid hormone replacement but do not respond well to digitalis or diuretics.

3. In general, pulmonary congestion is not present in hypothyroid patients.

4. The pericardial effusions occurring in hypothyroid patients have a much higher protein content than effusions associated with congestive heart failure. In addition, hypothyroid patients usually show other hallmarks of hypothyroidism and have associated laboratory values of a low thyroxine and an elevated TSH.

Recent studies have found that patients with severe congestive heart failure have a decreased number of TRs expressed in the heart.⁹ Furthermore, thyroid hormone levels are diminished

in the context of the nonthyroidal illness syndrome. Because genes that play an important role in the mediation of the normal contractile cycle, like SERCA, are markedly thyroid hormone responsive, the question has been raised if the down-regulation of the thyroid hormone system associated with the failing heart may contribute to the worsening of congestive heart failure.⁹ While this area is under current investigation, no firm conclusions related to a thyroidal contribution to heart failure in patients without primary hypothyroidism can be drawn.

Some studies in this area include a recent report indicating that children who underwent complicated surgery for congenital heart defects and exhibited a postoperative fall in T_3 benefited from intravenous T_3 administration 48 to 96 hours after surgery.⁵¹ Studies in adults related to overall benefits of T_3 administration after cardiac surgery were less conclusive; however, a decreased frequency of postoperative atrial fibrillation could be demonstrated in adults after coronary bypass surgery.⁵²

Long-standing hypothyroidism not only leads to decreased cardiac contraction but also has detrimental effects on the vascular system, effects that may promote the development of atherosclerotic lesions. An increased incidence of hypercholesterolemia can be identified in the hypothyroid patient population. Thyroid hormone has important influence on the enzymes that lead to cholesterol clearance.⁵³ The combination of an increased incidence of true hypertension in the hypothyroid patient population with the

increased occurrence of hypercholesterolemia probably accounts for the increased frequency of coronary artery disease in the hypothyroid patient population.

Treatment of Cardiovascular Symptoms in Hypothyroid Patients. Adequate thyroid hormone replacement is the most important therapeutic maneuver for hypothyroid patients with cardiovascular symptoms. All the changes in cardiovascular function improve and may revert to normal when a euthyroid status is reached. The increased occurrence of coronary artery disease in elderly hypothyroid patients, however, warrants a cautious approach to thyroid hormone replacement therapy. Levothyroxine is the drug of choice for replacement therapy. Its onset of action is slower than that of T_3 , and thyroid hormone levels are more stable. In patients with coronary artery disease, a starting dose of 25 μg per day is appropriate. This dose can be increased by 12.5 μg per day at 4- to 6-week intervals. If angina pectoris ensues after the patient has started replacement therapy, β -adrenergic blocking agents can be added to modify the increase in heart rate caused by T_4 replacement. Should severe coronary artery disease require surgery, this procedure can be performed before a full thyroid hormone replacement state is reached. Morbidity and mortality in such circumstances are not significantly increased.⁵⁴ The benefits of optimal thyroid hormone replacement include marked lowering of cholesterol and normalization of blood pressure. If cholesterol levels remain high

after adequate thyroid hormone replacement, additional cholesterol lowering, which often involves administration of a statin class of drug, should be undertaken. Similarly, if hypertension persists, blood pressure-lowering medication needs to be prescribed. The antiarrhythmic drug amiodarone can also induce a hypothyroid state⁴⁸ that does not present significant management problems and is adequately treated with appropriate thyroid hormone replacement.

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