Restoration of thyroid hormone balance: a game changer in the treatment of heart failure?

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Gerdes AM. Restoration of thyroid hormone balance: a game changer in the treatment of heart failure? Am J Physiol Heart Circ Physiol 308: H1–H10, 2015. First published November 7, 2014; doi:10.1152/ajpheart.00704.2014.—The link between low thyroid hormone (TH) function and heart failure is reviewed in the present report. The idea that TH dysfunction may contribute to diseases leading to HF has been discussed for over 60 yr. A growing body of evidence from animal and human studies, particularly in recent years, suggests that TH treatment may improve clinical outcomes. Indeed, if a similar amount of positive information were available for a newly developed heart drug, there is little doubt that large-scale clinical trials would be underway with considerable excitement. THs offer the promise of improving ventricular contraction and relaxation, improving coronary blood flow, and inhibiting atherosclerosis, and new results suggest they may even reduce the incidence of arrhythmias in heart diseases. Are the potential clinical benefits worth the risk of possible overdosing? After so many years, why has this question not been answered? Clearly, the concept has not been disproven. This review explores the body of clinical evidence related to TH dysfunction and heart failure, discuss insights into pathophysiological, cellular, and molecular mechanisms provided by animal research, and discuss what is needed to resolve this long-standing issue in cardiology and move forward.

heart failure; thyroid hormones; ventricular remodeling; treatment

MANY CRITICAL CARDIOVASCULAR FUNCTIONS are regulated by thyroid hormones (THs) (65). Most importantly, THs affect heart contraction, relaxation, and blood flow. Both hyperthyroidism and hypothyroidism lead to pathological conditions, with proper balance of THs necessary to maintain cardiovascular and metabolic homeostasis (91). Hyperthyroidism is less common but more easily identified by two characteristic symptoms in particular, tachycardia and heat intolerance. Hypothyroidism leads to reduced resting energy expenditure, weight gain, elevated cholesterol levels, reduced gluconeogenesis, and reduced lipolysis (91). Hypothyroidism can be more subtle with symptoms often attributed to other causes, such as aging, stress, lack of sleep, and poor physical condition. It is important to recognize, however, that chronic hypothyroidism alone can lead to heart failure (HF) with many manifestations and symptoms indistinguishable from those attributed to other heart diseases often leading to HF [e.g., impaired coronary blood flow, reduced left ventricular (LV) contractility and relaxation, reduced exercise tolerance, and depression]. A growing body of evidence suggests that we should be asking the following question: how much of the symptomology and cardiac manifestations observed in HF patients are due to the underlying diagnoses (e.g., ischemia, hypertension, diabetes, or idiopathic cardiomyopathy) and how much is due to low cardiac tissue TH levels? Figure 1 shows an overview of detrimental changes in the heart resulting from low TH function in heart diseases. The body of literature related to THs and cardiovascular disease is expansive and extends over many decades. Consequently, it is not possible to include the many thousands of relevant publications in a brief review. In this review, representative citations are given with the goals of providing a good understanding of the relevant literature, clearly describing the potential benefits of TH treatment/restoration (shown in Table 1), offering an explanation of how we got to the current clinical position on this topic and how we may move forward.

Clinical Evidence That Low Thyroid Function Contributes to Heart Diseases and HF

The idea that low TH function contributes to heart diseases and that treatment may improve outcomes has been around for many years. In fact, a 1950 study by Kountz (68) showed that desiccated TH treatment of three patient groups with a low metabolic rate resulted in dramatic reductions in cardiovascular mortality and rates of myocardial infarction (MI). In 1959, Barnes (7) showed that THs lowered high cholesterol levels effectively. He later showed a dramatic reduction in coronary artery disease in TH-treated patients (6). Many other positive reports over the years led to the inclusion of a TH component in the Coronary Drug Project. The Coronary Drug Project was a secondary prevention study of male survivors of MI that...
examined four lipid-lowering drugs (24a). Dextrothyroxine (D-T₄), the low-activity isomer of thyroxine (T₄), was selected for inclusion in the study rather than levothyroxine (L-T₄), the active form. In 1973, D-T₄ treatment was discontinued largely due to increased arrhythmias and higher mortality (116). The Coronary Drug Project results have had a long-lasting influence on the current attitude toward avoiding the use of THs in cardiovascular patients (37). However, it is seldom mentioned that the formulation of D-T₄ used in this study was high and later found to be contaminated with active L-T₄ (142). A more recent study (47) used another TH analog, diiodothyropropionic acid, to treat HF patients. While important cardiovascular benefits were noted, diiodothyropropionic acid was not well tolerated, and treated patients had increased heart rate, weight loss, and other symptoms suggesting that the dose may have also been too high. It is worth noting that both studies used TH analogs rather than native THs. It is unfortunate that lower doses were not also investigated in both studies. Relevant to this point, a MI study (89) in mice showed benefits with a therapeutic triiodothyronine (T₃) replacement dose but detrimental effects with T₃ overdosing. Importantly, many studies have shown that THs can be safely administered to HF patients with reported clinical benefits (26, 51, 86, 87, 104). Nonetheless, there are no long-term animal or human studies examining the effects of therapeutic TH treatment on cardiovascular mortality in HF.

Table 1. Cardiac benefits from restoring tissue triiodothyronine levels in heart disease

<table>
<thead>
<tr>
<th>Beneficial Effect</th>
<th>Specific Changes</th>
<th>Molecular Mechanism</th>
<th>References</th>
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<tbody>
<tr>
<td>LV systolic function</td>
<td>↑+dP/dt, restore normal heart rate, ↑LV ejection fraction</td>
<td>↑α-to-β-myosin heavy chain ratio, ↑β-adrenergic receptors</td>
<td>15, 73, 133</td>
</tr>
<tr>
<td>LV diastolic function</td>
<td>↓−dP/dt, ↓time constant of relaxation</td>
<td>↑Sarco(endo)plasmic reticulum Ca²⁺-ATPase, ↓phospholamban</td>
<td>15, 64</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>↓Coronary and peripheral vascular resistance</td>
<td>↑Akt/PI3K/NO signaling, ↑K⁺ channels, ↑Trα, ↓ANG II type 1 receptors</td>
<td>9, 13, 38, 80, 117</td>
</tr>
<tr>
<td>Arteriolar remodeling, angiogenesis</td>
<td>↑Expression of α-smooth muscle actin in small arterioles, angiogenesis</td>
<td>↑Akt/PI3K/NO signaling, ↑Trβ₁, αβ₂-integrin signaling</td>
<td>5, 17, 27, 29, 77, 79</td>
</tr>
<tr>
<td>Myocyte remodeling</td>
<td>↑Myocyte diameter without cell lengthening &gt; ↓LV diameter-to-wall thickness ratio &gt; ↓wall stress</td>
<td>↑Akt/PI3K/mTOR signaling?</td>
<td>11, 22, 39, 122</td>
</tr>
<tr>
<td>Myocyte survival</td>
<td>↓Myocyte apoptosis, secondary to ↓blood flow</td>
<td>↑Akt/PI3K/mTOR signaling</td>
<td>21, 22, 58</td>
</tr>
<tr>
<td>Serum lipids, calcium, and atherosclerosis</td>
<td>Improve serum lipid profile, ↓calcification, ↓atherosclerosis</td>
<td>↑Matrix Gla protein, ↑Trα₁, ↑NO signaling</td>
<td>6, 50, 56, 111, 131</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>↓Incidence and duration of atrial fibrillation associated with ↓atrial fibrosis</td>
<td>?</td>
<td>66, 144</td>
</tr>
<tr>
<td>Collagen/fibrosis</td>
<td>↓Interstitial collagen, ↓myocyte necrosis-related replacement fibrosis, ↓atrial fibrosis</td>
<td>↓Tissue inhibitors of metalloproteinase, ↑matrix metalloproteinase-1</td>
<td>20, 34, 45, 58, 139, 144</td>
</tr>
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LV, left ventricular; PI3K, phosphatidylinositol 3-kinase; NO, nitric oxide; TR, thyroid hormone receptor; mTOR, mammalian target of rapamycin.
THs are often said to promote a physiological, rather than pathological, stimulus to the heart (93). A recent study (1) in end-stage HF patients compared baseline tissues collected during LV assist device implantation with those collected at transplant with an intervening moderate physical exercise program in one group. Exercise-mediated improvement was associated with an increase in serum T3 and TH receptor (TR)α and Akt signaling with suppression of JNK signaling.

Many reports have suggested increased cardiovascular risk with borderline low TH conditions, such as low T3 syndrome and subclinical hypothyroidism (19, 50, 54–56, 71, 81), with improvement after TH treatment (55, 104, 107). More recent studies have actually shown increased mortality in HF patients with low TH function (24, 85, 128). However, results are controversial, with one meta-analysis showing no significant mortality risk (109) and two showing a link (48, 92). Potential reasons for these discrepancies will be discussed later. The high incidence of diagnosable hypothyroidism and borderline low TH conditions such as low T3 syndrome and subclinical hypothyroidism suggest that nearly half of heart patients could suffer from this condition (54). But, animal experiments have indicated that low cardiac tissue T3 levels may be present in the patients suffering from this condition (54). So, the number of afflicted patients could be much higher. Importantly, the incidence of low cardiac tissue T3 levels in heart diseases and HF is not known in humans at this time.

Patients suffering an MI often develop low serum T3. Worsening outcomes are linked to elevated serum reverse T3 (inactive form) levels and lower T3 (36, 78, 113). As we discuss below, the increase in serum reverse T3 levels suggests myocardial activation of an enzyme that deactivates THs.

Hypothyroidism and increased atherosclerosis/ischemic heart disease have been recognized for many years (6). Low TH function promotes endothelial dysfunction and vascular smooth muscle cell apoptosis, which can be inhibited by stimulation of TRα (131). Vascular calcifications are also inversely linked to THs (60, 84) even within the range of normal serum THs (145). TH treatment may reduce calcifications since it stimulates matrix Gla protein, a potent inhibitor of vascular calcification (111).

There is also evidence that low TH function may contribute to impaired coronary blood flow in “nonischemic” idiopathic dilated cardiomyopathy (DCM) (110, 130). Blood flow impairment appears to be at the microvascular level rather than with blockage of large coronary vessels. Interestingly, impaired coronary blood flow, reversible with TH treatment, has been shown in noncardiac patients with subclinical hypothyroidism (9, 126). So, the high incidence of borderline and low TH function in HF patients (54) as well as the presence of impaired coronary blood flow in DCM and subclinical hypothyroidism suggests that DCM patients may benefit from TH treatment. Indeed, the results of several clinical studies (86, 87) support this possibility. Pertinent to these human findings, our group (58) demonstrated that TH treatment restored impaired coronary blood flow, reversed cardiac fibrosis, and prevented myocardial loss in an animal model of DCM.

What Have We Learned From Animal Studies?

TH signaling. TH signaling is complex and becoming more so as new information arises. Since there are many comprehensive reviews on the topic (8, 32, 82, 91, 97), it will be discussed only briefly here. THs signal genomically through nuclear TRs. TRs bind to thyroid response elements (TREs) located in the promoter of target genes that are positively (e.g., α-myosin heavy chain) or negatively (e.g., β-myosin heavy chain) regulated by THs. TRs form homodimers or heterodimers with the retinoid receptor as they bind to TREs. Many coactivators and corepressors have been identified and are also involved in this nuclear signaling complex. While at least 10 TRs have been identified, TRα and TRβ are most prominent in the heart (8). TRs are located in the nucleus, cytoplasm, and mitochondria (8). While the most common TRs are functional with T3- and DNA-binding domains, others may lack one or both and generally have dominant negative effects on gene activity. An important effect of T3 on the heart is increased heart rate and contractility. These effects are at least partially due to T3 binding to a TRE in the β1-adrenergic receptor (β1-AR) gene (3) and the ability of T3 to increase β1-AR density (138). Pacemaker channel genes are also regulated by TRα with deletion of this receptor resulting in bradycardia (137).

Animal and human studies have generally shown downregulation of TRs in hypertrophy and HF, suggesting another mechanism by which TH function may be reduced even when serum hormone levels are normal (62, 63, 100). Nonetheless, there is considerable controversy in this area of research, particularly with regard to results from gene-targeted mouse studies that may represent more extreme changes than those typically occurring in real life (97). Impaired TRα signaling, in particular, likely plays a major role in cardiac dysfunction and adverse remodeling in heart diseases (88, 98). TRα is expressed in both nuclear and cytoplasmic compartments and may be involved in rapid signaling events by interactions with the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K), leading to nitric oxide (NO) activation (52, 93).

THs also signal through rapid, nongenomic mechanisms (8, 28, 115). Nongenomic signaling can occur within minutes and may be initiated in the cytoplasm or through membrane receptors (30, 52). Na+, K+, and Ca2+ channels may be affected in this manner (46, 93, 108). Important from the standpoint of this review, T3 can increase coronary blood flow within a matter of minutes, likely via the PI3K/Akt/NO pathway, with involvement of the ANG II type 2 receptor (13, 14, 38, 52). Endothelial TRα signaling has been shown to promote increased blood flow via an Akt/NO mechanism also involving adenosine receptors (117).

The PI3K/Akt/NO pathway is also involved in T3-mediated angiogenesis (17) and cardiomyocyte hypertrophy (70). Davis and colleagues (27, 28, 30) have demonstrated that T3 binding to an αβ2-integrin membrane receptor triggers angiogenesis via an ERK signaling mechanism. Work by Pantos et al. (102) has also implicated ERK signaling in T3-mediated changes in cardiac myocyte shape. It should be realized that at any given time there are complex ongoing interactions of genomic and nongenomic TH signaling mechanisms. In vitro experiments have been critical in providing new understanding to this area.

Type 3 iodothyronine deiodinase activation and fetal gene expression. Perhaps the most important finding from animal studies in recent years is that heart diseases, such as hypertension (127, 132), ischemia (94, 106, 114), and diabetes (134), trigger a reduction in cardiac tissue T3 levels. This appears to
be due largely to increased expression of type 3 iodothyronine deiodinase (DIO3), which converts T4 to reverse T3 and T3 to 3,5-diiodothyronine, inactive forms of THs. As a possible mechanism, reduced O2 bioavailability triggers hypoxia-inducible factor-1α, a strong inducer of DIO3 (105). It is known that starvation triggers low TH function, likely as a survival mechanism to reduce metabolism and conserve energy (33). Although speculative at this point, it is possible that the myocardium senses hypoxia in various heart diseases and is programmed to activate DIO3 and lower tissue T3 levels in response. However, like the situation with chronic activation of catecholamines in heart diseases, chronic hypothyroidism can also lead to HF and is associated with impaired coronary blood flow and maladaptive ventricular remodeling (121). Although excess T3 can stimulate increased O2 consumption, the hypothyroid heart is inefficient (10), and therapeutic restoration of myocardial T3 levels has been shown to improve the efficiency of myocardial O2 consumption during postischemia reperfusion (53, 67). The apparent upregulation of DIO3 in heart diseases suggests that T3 may be superior to T4 as a treatment. It is also possible that exogenous administration of T4 may inhibit T3 secretion by the thyroid gland. Coupled with impaired cardiac conversion of T4 to active T3, this may exacerbate the problem. A clinical study (78) has also shown that improved early and late functional recovery after MI tracks improved T3 and reduced T4. Importantly, TRα, the major TR in the heart regulating sarco(end)plasmic reticulum Ca2+-ATPase (SERCA) and myosin isoform expression, is highly regulated by T3 1 (97). Nonetheless, animal and clinical studies have shown cardiac benefits from either T3 or T4 treatment.

Another feature of low cardiac tissue T3 levels is the activation of genes normally expressed during fetal growth, which is also a characteristic finding in pathological hypertrophy and HF. Fetal gene reexpression in heart diseases may actually result from low tissue T3 levels. In particular, the switch from α-myosin to β-myosin leads to reduced systolic function, whereas downregulation of SERCA leads to reduced diastolic function. T3 also alters heart rate and contractility through interactions with the β-adrenergic system. As mentioned above, this may involve T3 binding to a TRE on the β1-AR gene (3) in addition to T3-induced changes in β1-AR density (138).

Bioavailability of T3. Transport of T3 into cells is ATP dependent, requiring thyroid hormone transporters (83). Monocarboxylate transporter (MCT)-8 and MCT-10 are expressed in the heart, with higher basal expression of MCT-10 (133, 134). In addition to serum-binding proteins, there are intracellular T3-binding proteins, of which μ-crystalline is highly expressed in the myocardium (133). In primary hypothyroidism induced by propylthiouracil in rats, the heart generally works to increase cellular T3 bioavailability by increasing MCT-10 and reducing μ-crystalline expression, whereas restoration of TH function with T3 treatment reversed these changes (133). For a review of myocardial diodinases, please see Pol et al. (105). Importantly, increased expression of DIO3 appears to be a common change in heart diseases, as described above. In diabetic rats, we noted reduced MCT-10 and increased DIO3, two changes that offer an explanation for the observed reduction in myocardial tissue T3 levels. It is not yet known if similar changes occur in ischemia or hypertension, conditions also associated with reduced myocardial T3.

Ventricular remodeling and myocyte remodeling/survival. At the beginning of my career, it was apparent that a comprehensive understanding of how cardiac myocytes remodel in physiological and pathological loading conditions was needed. After developing a precise approach to assess changes in cardiac myocyte shape from isolated myocytes, we then characterized differences in myocyte shape associated with growth, maturation, aging, sex (4, 118), altered thyroid conditions (11, 74), hypertension (12, 43, 136), MI (146), and DCM (40). We confirmed that pressure overloading triggers myocyte cross-sectional (width) growth (136) and compensated volume overloading leads to a proportional increase in myocyte length and width (75, 76). A common feature during the chamber dilation process in HF was cell lengthening from series sarcomere addition in the absence of transverse myocyte growth, a change that underlies the increase in wall stress (95, 119, 146). Hyperthyroidism induces myocyte hypertrophy with proportional myocyte growth, similar to physiological growth or compensated volume overloading (42). Akt signaling is likely involved in this physiological myocyte growth process (57, 70, 72). Overexpression of TRα1 alone has also been shown to induce myocyte hypertrophy (61). Hyperthyroidism initially leads to atrophy of myocyte width due to chamber unloading (74) but is later followed by cell lengthening from series addition of sarcomeres (121), a change specific to dilated HF, as noted above. These TH-related changes suggested that THs may be able to promote beneficial changes in pathological conditions. Indeed, TH treatment of rats with hypertension and dilated HF led to a specific pattern of growth in myocyte transverse dimensions only, a change that reduced systolic wall stress despite the continued presence of hypertension (122). In vitro experiments demonstrated that T3 inhibits myocyte apoptosis via an Akt-dependent mechanism (69). TH treatment during early post-MI remodeling inhibited myocyte apoptosis (21) and led to increased preservation of myocytes in the peri-infarct zone after long-term treatment (22). There was also a reduction in the myocyte length-to-width ratio due to transverse myocyte growth, a change that should reduce wall stress. Others have also reported beneficial remodeling in post-MI rats treated with THs (99) and improved chamber remodeling even after a 3-mo delay before the initiation of treatment (101). However, doses used in these rodent hypertension and MI studies are likely too high to consider in humans. Whether these beneficial effects on myocyte shape and preservation in hypertension and MI occur with low therapeutic doses of T3 have yet to be determined.

THs, vascular remodeling, and angiogenesis. The signaling responsible for TH-induced vasodilation is complex, with reports indicating a role for Akt/Pi3K/NO (13), increased vascular smooth muscle k+ channel activity via TRs (80), and inhibition of ANG II type 1 receptor signaling (38). Aside from the effects of THs on vasodilation, previous studies have suggested that altered TH states may have important effects on cardiac microvessels, including angiogenesis (23, 123–125). We noted an apparent loss of small arterioles in myocardium from chronically hypothyroid rats concomitant with impaired coronary blood flow (121). Later work suggested the apparent loss of small arterioles in hypothyroid myocardium is likely due to dedifferentiation of vascular smooth muscle rather than true arteriolar loss since restoration occurs within 3 days of T3.
treatment and precedes proliferation of vascular smooth muscle cells, pericytes, and endothelial cells (112). T₃ can induce sprouting angiogenesis in adult myocardium cultured from hypothyroid mice in a PDGF-Akt-dependent manner (17). Using a chick chorioallantoic membrane model, THs have been shown to promote angiogenesis via an α₁β₃ membrane integrin-MAPK-dependent mechanism mediated by fibroblast growth factor 2 (27, 90). A recent study (5) using cultured human microvascular endothelial cells showed that physiological levels of T₄ induced angiogenesis, likely via the α₁β₃ membrane integrin receptor. Other reports (22, 79) showed that THs promote physiological growth of cardiac arterioles and capillaries in hypertension and ischemia. TRβ has also been shown to play an important role in angiogenesis (79).

THs and collagen. Unlike pathological forms of hyperthyroidism, myocardial collagen concentration may be normal or reduced in hyperthyroidism (35, 140, 141). THs may accelerate the breakdown of collagen types I and III by increased matrix metalloproteinase-1 activity from suppression of endogenous tissue inhibitors of metalloproteinase (45). Increased collagen accumulation in hypothyroidism has been reported, possibly via regulation of collagen gene expression through TRs (20, 34, 139, 144). However, right ventricular fibrosis related to pulmonary hypertension resulting from hyperthyroidism has been noted (41) along with significant myocardial fibrosis in long-term hyperthyroidism (135). In those instances, collagen increases may have been related to sustained mechanical overloading rather than direct actions of THs. A number of studies have suggested that TH treatment tends to inhibit or possibly reverse myocardial fibrosis in heart diseases (22, 58, 134). Low-dose TH treatment will likely produce similar results in humans with heart diseases, but this has not been clearly demonstrated.

THs and arrhythmias. It has long been recognized that hyperthyroidism can lead to increases arrhythmias (103). Some clinical reports have also linked hypothyroidism and subclinical hypothyroidism to increased incidence of arrhythmias (120, 129), but others found no relationship (59). Considering the unknown status of cardiac tissue T₃ levels in patient studies and the likelihood that most cardiac patients may have low tissue T₃ levels despite normal serum status, discrepancies should not be surprising. To better address this under controlled conditions in rats, we examined induced arrhythmias in hypothyroidism, euthyroidism, and hyperthyroidism using a previous protocol that confirmed low, normal, and elevated cardiac T₃ levels, respectively (73). It was found that both hyperthyroidism and hypothyroidism led to increased susceptibility to arrhythmias (144). The duration of atrial fibrillation was also longer in hypothyroid rats. The same T₄ treatment protocol (slow-release subcutaneous pellets) was recently used to treat rats after MI. As expected, MI rats were more susceptible to arrhythmia induction and T₄ treatment reduced arrhythmia induction significantly. The reduction in arrhythmias by T₄ was associated with reduced atrial fibrosis (143). This issue certainly merits clinical exploration.

Associations among serum THs, cardiac T₃ levels, and heart function. We examined the restoration of cardiac T₃ levels and associated changes in LV function in hypothyroid rats treated with either T₄ (73) or T₃ (133). In both cases, the doses of T₃ or T₄ needed to fully restore LV function resulted in higher than normal serum hormone values. This was disconcerting since providing high doses of THs to restore cardiac tissue T₃ levels in HF is not a realistic clinical option. As a result of these findings, we realized it was necessary to determine whether or not clear pathophysiologial benefits occur with a low-dose oral T₃ treatment protocol that would be acceptable in a clinical setting. In these experiments, a T₃ dose leading to feedback inhibition of thyroid-stimulating hormone (TSH) and usually T₄ but insignificant changes in serum T₃ levels and no change in heart rate was used. Using this approach, T₃ treatment of a rat model of mild diabetes (streptozotocin + nicotinamide) with stable body mass was examined (134). Diabetic rats had low cardiac tissue T₃ levels, systolic and diastolic dysfunction, and reduced arteriolar density. Low-dose T₃ safely restored cardiac T₃ and prevented LV dysfunction and arteriolar loss. Further work is needed to determine the mechanisms by which THs promote arteriolar remodeling in diabetes. Preliminary data from other rat HF models using the same safe oral T₃ protocol have suggested similar beneficial results (unpublished observations). Consequently, it appears that unlike the situation in primary hypothyroidism cardiac tissue hypothyroidism secondary to heart disease can be safely restored with low doses of T₃, resulting in significant benefits.

Thyroid Dysfunction and Diabetes Mellitus

Low TH function and diabetes mellitus are the two most common endocrine disorders in clinical practice, and both are linked to a higher incidence of HF (31, 96). Subclinical hypothyroidism has been linked to nephropathy and cardiovascular diseases in patients with diabetes mellitus (16). A comprehensive overview of the association between TH dysfunction and diabetes mellitus has been provided by Hage et al. (49). Of particular importance to the present review, impaired PI3K/Akt signaling is a hallmark feature of insulin resistance, and THs clearly promote beneficial changes in this signaling cascade (25). Clearly, more studies examining the potential benefits of TH treatment in diabetes mellitus are warranted.

Understanding Limitations and Moving Forward

A common limitation of research in this field is determining direct effects of THs versus those related to hemodynamic alterations secondary to THs. In most studies, this may not be clear, and the observed changes are likely a combination of both. Nonetheless, many in vitro studies described in this article have clearly demonstrated direct effects of THs on myocyte growth/survival and vessel remodeling. It is important to note that from a clinical standpoint the overall effect on the individual is more important than whether it is a primary or secondary effect of TH treatment.

Aside from the presence or absence of heart disease, the decision to treat borderline low TH dysfunction is contentious. In comments from a joint consensus statement from United States endocrine societies, it was noted that their recommendation regarding treatment of subclinical hypothyroidism was “based primarily on a lack of evidence for benefit rather than on evidence for a lack of benefit” (44). With the additional fear of arrhythmias from overtreatment, it is not surprising that few clinicians consider treating borderline low TH conditions in heart patients.

It is clear that current serum TH assays do not provide ideal guidance for treatment. Additionally, clinicians rarely know...
what “normal” values were for a given HF patient before s/he became sick. Individual diagnoses based on TH values within the normal reference range for a group may also be misleading for a given individual who might normally test in the upper or lower quartile before becoming sick. For instance, if the lower quartile for TSH were normal for a given patient who moved to the upper quartile after developing HF, this patient could very well be overtly hypothyroid despite testing normal by serum assays. This situation is likely more common for HF patients who demonstrate an unusually high incidence of borderline hypothyroidism. Assays from peripheral blood may also be a poor predictor of cardiac tissue TH levels since coronary sinus blood draining the heart is diluted by ~20-fold as it joins peripheral blood. It would certainly be helpful if a serum biomarker tracking with low cardiac tissue T3 levels were available to guide treatment. Since this tissue hormone imbalance likely occurs early in heart disease, significant preventative benefits should also result. The shortcomings of serum TH levels as a predictor of cardiac tissue TH status undoubtedly contributes significantly to conflicting clinical reports on this topic.

Despite the overwhelming body of positive evidence noted above, a reasonable and knowledgeable clinician may have important concerns about proceeding with treatment. What form should be used T3, T4, or both? Since it is not feasible to measure cardiac tissue T3 levels in patients without performing biopsies, how do you know when tissue T3 levels are restored with treatment? We do not know what the long-term effects of treatment are since there are currently no mortality studies available in animals or humans.

Using feedback inhibition of TSH as a guide, our laboratory has demonstrated in animal models that low-dose T3 can restore depressed cardiac T3 levels without significantly elevating serum T3, with remarkable cardiovascular benefits. This seems like a reasonable approach to use in humans with HF and evidence of low TH function, including subclinical hypothyroidism and low T3 syndrome. It is likely that responders would be quickly recognized since T3 improves coronary blood flow within minutes. When considering the likely upregulation of DIO3 in heart disease and subsequent excess conversion of T4 to reverse T3, it seems logical that T3 administration may deliver more active hormone to cardiac tissue than T4. Nonetheless, clinical data have suggested that both forms work. Importantly, evidence suggests that native THs can be used safely and effectively, which would lead to considerable healthcare savings. With another person dying of HF every 5 s in the world, there should be a sense of urgency to move forward with such a promising treatment.

DISCLOSURES

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THYROID DYSFUNCTION AND HEART FAILURE

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