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Is There A Safe, Therapeutic Window for Thyroid Hormone Therapy in Heart Failure?

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Editorial

Cardiovascular researchers are searching for new heart failure (HF) drugs that improve LV systolic/diastolic function and coronary blood flow, while inhibiting cardiac fibrosis, inflammation, re-expression of fetal genes, atherosclerosis, and arrhythmias. Indeed, a drug that safely accomplished all of the above would be front page news. Surprisingly, we have had such a drug in our arsenal for almost 80 years but are afraid to use it [1]. Is that fear justified?

In 1950 Kountz [2] showed a dramatic reduction in cardiovascular mortality and rates of myocardial infarction (MI) in three patient groups with low metabolic rate that were treated with desiccated thyroid hormone (DTH) [2]. Rather than confirming the DTH effect in a larger population, the most influential follow up trial, the Coronary Drug Project (CDP), overdosed patients with the TH analog D-T4 (D-thyroxine; compound also contaminated with active L-T4; see review for further details) [1]. The D-T4 limb of the CDP was discontinued due to an increase in arrhythmias and mortality. A similar conclusion was reached from the DITPA (3,5-Diiodothyropropionic Acid) HF trial, which also used a TH analog [3]. Overdosing likely occurred in the DITPA study too, with dose selection based on "maximization of the probability of seeing an effect by use of the presumed maximum tolerated dose" and observation of increased heart rate, diarrhea, weight loss, and fatigue in treated patients. Thus, the prevailing opinion that THs are too dangerous for cardiac patients appears to be largely based on studies that did not use actual THs, but instead overdosed patients with TH analogs.

An overwhelming body of new evidence has provided important insight since the current clinical position was established [1]. Animal studies by Warner Simonides and others have shown that heart diseases, such as MI, hypertension, and diabetic cardiomyopathy produce changes in cardiac deiodinases that lower tissue triiodo-L-thyronine (T3) levels [1,4]. Chronic hypothyroidism (Hypo) alone eventually leads to HF, with impaired coronary blood flow and chamber dilatation from excessive myocyte lengthening, a hallmark of dilated HF [5]. Cumulative findings raise the possibility that fetal gene re-expression, a ubiquitous feature of heart diseases, may actually be due to cardiac tissue Hypo. Recent clinical studies have shown increased mortality in HF patients with low TH function [6,7]. Pingitore A, et al. [8] and others have published short-term studies demonstrating major improvements in HF patients treated with T3 or T4. Perhaps, we should be asking the question-"How much of your heart disease is due to the diagnosis and how much is due to a treatable hormone imbalance?" It is worth noting here that cardiac manifestations from low cardiac T3 are essentially indistinguishable from HF symptoms produced by other causes.

So, what are the obstacles for translation? Certainly, there is a lack of financial incentive. Reasonable clinicians will also ask the following: Should we use T3, T4, or both? Is there a safe treatment/monitoring protocol that can be implemented? While it is extremely likely that low cardiac tissue T3 also occurs in human HF, this has not been confirmed. Can cardiac tissue T3 levels be safely restored and how would you know without doing a biopsy?

A brief look at the TH analog literature is enlightening, revealing a general belief by these experts that THs are too dangerous for HF patients- TH analogs are needed. But, this belief has never been proven. Over the past 5 years, we have focused on this important issue. First, a better understanding of how cardiac tissue normally regulates T3 bioavailability during altered TH states was needed. Using Hypo rats treated with graded doses of T3 or T4, Hypo increased cardiac expression of a major T3 transporter, MCT10, while altering expression of deiodinases in a manner that would improve T3 production. The opposite occurs in hyperthyroidism. Consequently, it appears that the heart normally works to restore proper TH balance [1]. A tight relationship was also observed between tissue T3 levels and LV functional parameters, suggesting that changes in heart rate are an excellent surrogate for cardiac T3 levels in the absence of drugs affecting chronotropy. However, cardiac tissue T3 levels were not restored by serum normalizing doses of T3 or T4 alone. Higher doses were needed. Of note, studies by Gabrielle Escobar suggested that a combination of T3 and T4 are needed to normalize both serum and cardiac tissue T3 levels simultaneously in Hypo rats. But, is this potential serum/cardiac tissue mismatch in primary Hypo also true for cardiac tissue Hypo secondary to heart diseases? Confirming the presence of a therapeutic window for T3 or T4 (the current treatment standard as Synthroid) treatment is critical since use of excess doses of THs in HF patients is dangerous.

Oral T3 treatment was used in a series of HF studies in rats to explore a therapeutic window. T3 was chosen since, theoretically, there should be a better chance of directly restoring tissue T3 in light of known changes in deiodinases induced in heart diseases. The upper limit was determined by the dose that triggered an increase in heart weight and heart rate. To summarize results from these studies, oral T3 doses between 3-8 µg/kg/day provided significant improvement in many cardiac parameters. Doses within this target range generally showed expected feedback inhibition of TSH and often T4, but no significant change in serum T3 (except restoration when serum T3 was below normal). Doses over 8 µg/kg/day led to an increase in heart weight and heart rate. Please note that these are actual working doses for rats and may seem high due to reduced absorption from ad lib food consumption.

In a rat model of diabetic cardiomyopathy, a T3 dose of 3 µg/kg/day restored cardiac tissue T3 levels, prevented LV dysfunction,

maladaptive changes in TH transporters and deiodinases, re-expression of fetal genes, and loss of coronary arterioles. Importantly, untreated animals had normal serum TH levels and T3 treatment did not elevate serum free T3 or total T3 levels. Although rats remained diabetic, T3 treatment completely prevented development of heart disease [9]. For a similar group of patients, TH treatment would have never been considered as a treatment option. Clearly, a serum biomarker for cardiac T3 levels would be helpful. In the second study, Spontaneously Hypertensive HF rats were treated with a similar T3 dose (4 µg/kg/day) for 1 yr starting at age 12 months. In the face of sustained, life-time hypertension, T3 treatment showed a strong trend for improvement of diastolic function and cardiac fibrosis was not significantly different from normotensive controls. Oral T3 treatment normalized cardiac tissue T3 levels, serum T3 levels, and heart rate, with no additional increase in heart weight [10]. This study suggests possible benefits from normalizing TH function in patients with HF with preserved ejection fraction, a lethal condition which currently has no effective treatments. In the final study, MI rats were treated orally with 6 µg/kg/day T3 for 2 months. Treatment led to improved LV function, a reduction in inducible tachyarrhythmias, and reversed expression of many pathological genes [11]. Again, in each of these 3 studies in different models of HF, oral T3 led to major benefits without increasing heart rate, heart weight, or serum T3 levels above normal.

It is worth noting that previous studies from our lab showed increased susceptibility to inducible tachyarrhythmia in hypothyroid rats [1] and protection from arrhythmias (atrial fibrillation) with T3 or T4 treatment of MI in rats [1,11]. Some clinical studies also suggest increased risk for arrhythmias in subclinical hypothyroidism [12,13]. This issue certainly merits clarification since the current fear of arrhythmia induction with TH treatment of HF may actually be leading to more arrhythmias in some cases.

Addressing what may be the biggest obstacle to translation, these recent oral T3 studies clearly demonstrated a safe treatment window and treatment/monitoring protocol, effective in three different rat models of HF. Importantly, efficacy was shown with low T3 doses that did not elevate serum T3 levels but showed some inhibition of TSH. Since many HF patients have diagnosable low, or borderline low, TH conditions and will likely benefit from restoration of cardiac tissue T3 levels, this information offers important insight for clinical trials. Many questions remain, such as which form of TH to use. Clinical studies have shown favorable treatment effects with either T3, T4, or both.

There is reason for optimism in finally resolving the question of whether to treat low TH function in HF with trials such as ThyrAMI (T4 treatment of acute MI) and Iervasi's T3 treatment THiRST study (Thyroid Hormone Replacement Therapy in ST Elevation MI) which are underway [14]. Potential benefits from treating subclinical Hypo may also be resolved in the Thyroid hormone Replacement for Undertreated older adults with Subclinical hypothyroidism (TRUST) trial [15]. Clearly, there is forward movement on resolving an issue that simply will not go away. Our recent studies in rats show that, for the heart, it appears that a little bit of TH goes a long way, and it can be done safely. It is important to determine if the same is true for humans.

A good starting point would be to finally repeat the study by Kountz [2] in a larger patient population to confirm if reduced mortality is indeed an achievable goal in the treatment of HF with THs.

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