Thyroid Hormone Repletion in Patients with Congestive Heart Failure

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A. Study Purpose and Rationale

Thyroid hormone has many effects on the cardiovascular system. It is closely linked to heart rate, cardiac output and systemic vascular resistance. Thyroid hormone is thought to work directly and indirectly, through nuclear receptors, on the cardiac myocyte. It acts directly on vascular smooth muscle and cardiac myocytes by altering the performance of sodium, potassium, and calcium channels in the heart, resulting in increased chronotropy, inotropy and vasodilatation. The indirect actions are through nuclear receptors, altering genetic expression.1,2 Whereas hyperthyroidism results in an increased cardiac output, tachycardia, and palpitations, hypothyroidism can result in bradycardia, mild hypertension, and a narrowed pulse pressure. Clinically, hypothyroid patients present with symptoms including weakness, dyspnea, edema, dryness of the skin, and cold intolerance.

Many symptoms of heart failure symptoms overlap with symptoms of hypothyroidism, making it impossible to distinguish clinical heart failure from hypothyroidism in certain situations.3 A common entity among patients with congestive heart failure is a “low triiodothyronine (T₃) syndrome.” Low T₃ syndrome is defined as having low T₃ levels and normal thyroid stimulating hormone (TSH) and thyroxine (T₄) levels. This syndrome is thought to be the result of a decreased availability of the enzyme 1,5 iodothyronine deiodinase, which converts T₄ to T₃. Since T₃ is the bioactive form of thyroid hormone for cardiomyocytes, it is possible that some of the symptoms in patients with heart failure and a “low T₃ syndrome” are attributable to a low level of T₃ reaching the cardiac myocytes. One theory for the low T₃ syndrome is that enzyme function may be impaired secondary to passive hepatic congestion, reducing the enzyme activity, leading to low free T₃ index and high reverse T₃.4 Theoretically, the low T₃ syndrome may enhance survival during illness by decreasing whole body energy expenditure and rates of protein catabolism in a state of heart failure. Practically, it may worsen heart failure symptoms as hypothyroidism is known to impair the intrinsic contractile state of the myocardium.5 Studies have shown a correlation between New York Heart Association class and the level of T₃. There is a high risk of hypothyroidism and low T₃ syndrome in patients regardless of treatment with amiodarone, which appears to correlate with disease severity.6 A low free T₃ index/reverse T₃ ratio has been associated with poor ventricular function and nutritional status has been shown to be a strong predictor for short-term outcome in patients with advanced heart failure.5

Preliminary research has been done with thyroid hormone supplementation in patients with heart failure, indicating clinical improvements in heart failure symptoms with thyroid hormone repletion. Animal models have shown that thyroid hormone or thyroid hormone analogues improve ventricular performance and reduced end diastolic pressure ⁷,⁸,⁹ In a study of 23 human patients with New York Heart Association (NYHA) Class III to IV heart failure secondary to ischemic or idiopathic cardiomyopathy, infusion of IV bolus dose of T₃ with or without a 6-12 hour infusion resulted in an increase in cardiac output, with a reduction in systemic vascular resistance.¹⁰ One human, randomized placebo controlled trial has been done replacing L-thyroxine in patients with idiopathic dilated cardiomyopathies, NYHA Class II to IV, in patients with normal thyroid function tests. After treating patients with 100 micrograms of L-thyroxine every day for three months, patients did not show evidence of chemical hyperthyroidism. Cardiac performance improved, resting cardiac output increased, systemic vascular resistances decreased, and functional capacity markedly improved.¹¹ Despite concerns that thyroid hormone repletion will result in tachyarrhythmias or increased cardiac ischemia in a population of patients with congestive heart failure, repletion of either intravenous
T₃ or oral T₄ in congestive heart failure patients and intravenous T₃ in peri-bypass surgical patients have not shown significant increases in sustained arrhythmias or ischemia.

Studies have shown that repleting thyroid hormone, either in the form of oral or intravenous T₄ or intravenous T₃ are effective in improving the hemodynamics, exercise tolerance, and symptoms of patients in congestive heart failure who have low T₃ syndrome. It is thought that low T₃ syndrome is a result of poor conversion between T₄ to T₃, although this mechanism has never been proven. One would deduce that repletion of T₃ would be more effective in this patient population. Despite this conversion problem, studies have proven efficacy of both T₃ and T₄ replacement. A current ongoing study is looking at the effect of repleting T₃ orally on exercise tolerance. Disadvantages of treating with T₃ include wide fluctuations in serum levels and rapid metabolism. The one prospective, placebo controlled randomized study in this patient population indicates that repletion of thyroxine is effective in improving exercise tolerance. This study only had 20 subjects who had idiopathic cardiomyopathies. The present study is being done to compare oral T₃ and oral T₄ repletion in patients with Class II to Class III congestive heart failure and a “low T₃ syndrome.” The purpose is to determine if they are equally effective in improving exercise tolerance in patient with heart failure.

B. METHODS

a. Study Design

This study is a prospective, randomized, placebo controlled, double blinded, parallel arm study. The three study arms are treatment with Cytomel (triiodothyronine, T₃), treatment with Synthroid (L-Thyroxine, T₄), or placebo. Patients will be randomized in a 1:1:1 ratio. The primary end-point is exercise tolerance as measured by VO₂ maximum on a cardiopulmonary stress test. Based on a previous study by Morruzi, thyroid hormone repletion resulted in mean effect size in VO₂ maximum of 2.4 ± 3.2 ml/kg/min in a patient population with idiopathic dilated cardiomyopathy. We estimated that 30 patients would be needed in each group in order to detect a significant difference in response rates among the groups at a power of 80% and a 5 percent level of significance.

Secondary endpoints include ejection fraction as measured by echocardiography, thyroid function tests, including thyroid stimulating hormone, T₄ levels, T₃ levels, reverse T₃ levels and rate of arrhythmias, recorded by percent increase of ventricular ectopic beats, episodes of sustained or non-sustained ventricular tachycardia, or onset of atrial flutter or atrial fibrillation.

After signing a consent form, patients will be randomized to receive placebo (Group 1), liothyronine (Group 2) or levothyroxine (Group 3). Randomization will be stratified based on whether or not the patient is being treated with a beta blocker. After randomization, patients will undergo the following:

- Complete history and physical exam, including the medications that the patient is currently taking, BP, and pulse
- ECG
- Assessment of NYHA of heart failure
- Baseline laboratory values including thyroid function tests, liver function tests, chemistry 7, as well as an INR and digoxin level for patients on warfarin and digoxin. All laboratory tests will be run according to the typical protocol in the core lab of Columbia Presbyterian Medical Center and results will be obtained and interpreted by physician blinded to the patients. The protocol for TSH levels is the Ultrasensitive TSH2 by a microparticle enzyme immunoassay, the T₄ assay is a Flourescein Polarization Immunoassay, the T₃ assay is a microparticle enzyme immunoassay. All assays are run on the Abbott/Axsyn system.
- Cardiopulmonary stress test- Two initial cardiopulmonary exercise tests will be performed. The first will be to familiarize the patients with the equipment and the second will be for data
collection. Patients will exercise on a bicycle or treadmill on a graded work rate protocol. Work rate will be gradually increased to symptoms limited maximum. Expired gases will be analyzed throughout the exercise to determine peak oxygen uptake and anaerobic threshold. Heart rate and blood pressure will be monitored throughout the test. Subjects will walk/run on a treadmill or cycle on a bicycle ergometer. During the test the work rate will increase incrementally or continuously as a ramp function. Heart rate will be recorded continuously throughout the test and expired gas analysis will be performed on a breath-by-breath basis via a mouthpiece. Blood pressure will also be monitored every two to three minutes during the exercise. Subjects will be asked to continue as long as they can to produce a maximum effort but can stop the exercise for any reason whatsoever. Expired gas analysis will be performed with a commercially available Sensormedics Vmax metabolic chart, with oxygen and carbon dioxide measured continuously from the mouthpiece. Volume calibration will be performed with a 3 liter calibration syringe before each test. The gas analyzers will be calibrated prior to each test with commercially prepared gas mixtures of known concentration certified to within 0.02%. Peak oxygen uptake will be defined as the highest value of oxygen uptake attained in the final 20 seconds of exercise.¹⁵

- Echocardiogram
- 24 hours Holter monitor will be done for baseline characteristics

Initial liothyronine (T₃) doses will be 5 microgram (mcg) per day and initial levothyroxine (T₄) dose will be 20 mcg. After a ten day period, dose of T₃ will be increased to 5 mcg twice a day and T₄ to 40 mcg per day. After another 10 day period, dose of T₃ will be increased to 10 mcg every morning, 5 mcg every evening and the dose of T₄ will be increased to 60 mcg per day. After 10 more days, T₃ will be increased to 10 mcg twice a day and T₄ will be increased to 80 mcg per day. After 10 more days, the dose of T₃ will be increased to 12.5 mcg twice a day, the final stable dose and T₄ will be increased to 100 mcg per day. All patients will take one pill a day during the initial ten day period and from then onward, each patient will receive two pills a day, either with or without active drug based on the dosing schedule above. Pills will be made in the research pharmacy in capsule form so that the pills containing liothyronine, levothyroxine, and placebo look exactly the same, regardless of dose. After the titration phase is over, patients will be maintained on their goal medication dose for the next 12 weeks.

During each of the initial ten day “titration” visits and at a clinic visit every two weeks thereafter, patients will have:
- An interim history which will include assessment for adverse effects, hospitalizations and or emergency room visits, compliance with medications,
- Physical exam
- Laboratory evaluation, including thyroid function tests, drawn before the morning dose of study medication, digoxin and warfarin levels for any patients on those medications. Treatment dose will be adjusted if patient develops signs of clinical hyperthyroidism, or laboratory abnormalities consistent with hyperthyroidism, including a suppressed TSH or abnormally elevated T₄ level
- ECG done
- 24 hour holter monitor will be repeated on day 40 and week 10 of the study.

The study will last for about 17 weeks and 5 days, comprised of 40 day titration period plus a 12 week maintenance period. At the completion of the study, in addition to studies done at the typical clinic visit (as described above), patients with undergo:
- echocardiogram
- cardiopulmonary stress test
- assessment of NYHA classification of CHF
b. Statistical Analysis

All data will be presented as mean ± standard deviation. Comparisons between three or more groups will be made using an ANOVA test for data distributed evenly and statistical significance will be assumed at a p value of <0.05.

c. Study Drugs

Study drugs include oral levothyroxine (Synthroid, T₄) and oral liothyronine sodium (Cytomel, T₃). Both drugs are approved by the FDA for the treatment on hypothyroidism.

Dosing regimen- both drugs will be titrated up over a 40 day period. Patients in the Liothyronine arm will begin with a 5 microgram dose over the first ten days. The dose will be increased to 5 micrograms twice a day after ten days. On study day 20, liothyronine will be increased to 10 micrograms in the morning and 5 micrograms at night. On study day 30, liothyronine will be increased to 10 micrograms twice a day, and on study day 40, the dose will be increased to 12.5 micrograms twice a day. For the remaining 8 weeks of the study, patients will be treated with a dose of 12.5 micrograms twice a day. This dose represents a low dose of liothyronine.

Patients in the levothyroxine group will start with a medication dose of 20 micrograms per day, which will be increased to a dose of 40 micrograms every day on day 10 of the study, 60 micrograms on day 20, 80 micrograms on day 30, and 100 micrograms on day 40. For the remainder of the study, patients will receive 100 micrograms per day, which represents a low dose of levothyroxine.

The most frequent, major adverse effects of liothyronine sodium include arrhythmias (6%) and tachycardia (3%). Cardiopulmonary arrest, hypotension, and myocardial infarction have occurred in approximately 2% of patients. Approximately 1% of patients or fewer have experienced hypertension, congestive heart failure, or phlebitis. Other common adverse reactions include tachycardia, nervousness, insomnia, tremor, diarrhea, headache, angina, weight loss and diaphoresis. U.S. Food and Drug Administration's Pregnancy Category A (Prod Info Triostat(R), 1997).

Levothyroxine replacement can potentially aggravate cardiovascular disease. Long-term levothyroxine (T₄) suppressive therapy contributed to decreased physical exercise capacity and cardiac reserve in 10 patients compared with 10 healthy controls (Biondi et al, 1996). The patients had received T₄ (mean dose 2.31 +/- 0.13 micrograms/kilogram/day) for 5 to 9 years. Other possible side effects include hypertension, angina, congestive heart failure, palpitations, increased appetite, tachycardia, nervousness, tremor, weight loss, diaphoresis, diarrhea, abdominal cramps, insomnia, fever, headache, alopecia, thyrotoxicosis, adrenal insufficiency, and hypersensitivity reactions. U.S. Food and Drug Administration's Pregnancy Category A (Prod Info Synthroid(R), 2002).

d. Subject Selection

Inclusion criteria
- Male or non-pregnant female older than 18 years old
- Ejection Fraction of < 35%, recorded within 6 months of randomization
- No surgical intervention or initiation of Beta Blocker since the last EF was recorded
- Patients with Class II or III heart failure
- Patients in sinus rhythm - Low T₃ syndrome, as defined by normal TSH (0.34-4.25 MIU/ml) and T₄ (5.41-11.66 mcg/dl) levels with low T₃ levels (less than 80ng/dL)
- On Stable medications for congestive heart failure over the past 1 month

Exclusion Criteria
- Patients with Class I or Class IV Heart Failure
- Patients with an initial holter recorder with complex ventricular arrhythmias, defined as greater than 3 ventricular premature complexes in succession and/or sustained ventricular tachycardia
- Etiology of CHF due to hypo or hyperthyroidism, restrictive, obstructive or hypertrophic cardiomyopathies, potentially reversible forms of cardiomyopathy, myocarditis, women with heart failure during 12 months following childbirth, amyloid or pericardial disease
- Patients on intravenous inotropic drug infusion, intra-aortic balloon pump or left ventricular assist device
- Myocardial infarction within the past 6 months
- Subjects with a basal TSH less than 0.5 mU/L
- Systolic blood pressure greater than 150 mm Hg
- Stable or Unstable angina
- Patient’s repleted with thyroid hormone
- Patients on amiodarone or oral steroids
- Patients who have received or are likely to receive a heart transplant within six months of screening
- Pregnant or lactating women or women planning on becoming pregnant
- Surgical revascularization procedures, therapeutic valvular repair left ventricular reduction surgery or cardiomyoplasty planned
- Patients with history or arrhythmia
- Minors, mental patients, prisoners, institutionalized patients and patients unable to give informed consent

This study will not be restricted by gender, ethnicity or race.

e. Recruitment of Subjects

Patients will be recruited from the Heart Failure Center at CPMC. Eligible patients are those with an EF of less than 35%, with NYHA Class II to III heart failure, with thyroid function tests consistent with the “low T3 syndrome” as patients with congestive heart failure should have a full thyroid panel evaluation during their initial work up of heart failure. Patients with a low T3 syndrome typically have a normal T4 and TSH level and a low T3 level. Initially, the patient’s primary cardiologist will discuss the possibility of participating in the study with the patient. If the patient agrees, the primary investigative team will approach him/her. The team will explain the study in more detail, including the risks and benefits of participating in the study.

C. Confidentiality of Study Data

All study data will be coded, by a unique coding system and data will be stored in a secure location, accessible only to the investigators.

D. Potential Conflict of Interest

None of the investigators, nor the University have a proprietary interest in the drug under investigation or might stand to benefit financially in any other way from the results of the investigation, that information must be disclosed.

E. Location of the Study
Studies will be conducted in the clinical care areas, including the Heart Failure Center, the Cardiopulmonary stress lab, and the Echocardiography suite.

F. Potential Risks

No adverse events, including arrhythmias or ischemia have been observed in studies administering T₃ or T₄ to heart failure patients.⁶,¹⁰,¹¹,¹² Treatment will be discontinued in patients if patient develops symptoms consistent with angina, there is evidence of a 25% increase in ectopic ventricular beats, or any evidence of sustained ventricular arrhythmias. Furthermore, treatment dose will be adjusted if patient develops signs of clinical hyperthyroidism, or laboratory abnormalities consistent with hyperthyroidism, including a suppressed TSH or abnormally elevated T₄ level.

G. Potential Benefits

Potential Benefits of this study include symptomatic improvement of heart failure symptoms and improved exercise tolerance. This study may add to alterations in standard heart failure treatment in the future.

H. Alternative Therapies

Standard medical heart failure therapy.

I. Compensation to Subjects

Subjects will not receive any compensation for participating in this study.

J. Costs to Subjects

Patient will not incur any costs as a result of participating in the study.

K. References

⁵ Hamilton, MA, Stevenson, LW Luu, M, Walden JA. “Altered Thyroid Hormone Metabolism in Advanced Heart Failure.” JACC. 1990; 16: 91-95.
⁷ Mahaffey, KW, Raya TE, Pennock GD, Morkin E, Goldman S. “Left Ventricular Performance and Remodeling in Rabbits After Myocardial Infarction.” Circulation. 91 (3) 794-801.


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15 IRB Protocol 14396 “Normal Cardiovascular Response During Cardiovascular Response During Cardiopulmonary Exercise Testing.”