MEDIUM TERM EFFECTIVENESS OF THYROXINE TREATMENT IN CONGESTIVE CARDIAC FAILURE (CCF)

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ABSTRACT

Objectives: *To test the medium term efficacy of L-thyroxin compared with placebo and to find out if later effects are obtainable in patients of CCF.*

Material and Methods: *It was an experimental, randomized, double blind clinical trial, recruiting patients of CCF visiting O.P.D or admitted in Fauji Foundation Hospital Rawalpindi. The subjects were in two groups i.e thyroxin group (cases) and placebo group (controls) of 30 each. Pulse rate, E.C.G findings/ryhthm, cardiothoracic ratio on CXR, holter findings if applicable, ejection fraction on echocardiography, T_3 T_4 T_{SH} levels, weight were the parameters compared.*

Results: *There was significant difference between the mean ejection fractions of patients with congestive cardiac failure after receiving thyroxin for 3 months. There was no significant difference between the mean ejection fractions of patients with congestive cardiac failure after receiving placebo for 3 months.*

Conclusion: *In heart failure a three month treatment with thyroxin has beneficial effects in terms of increasing the ejection fraction of the failing heart without inducing undesired effects like rhythm disturbances.*

Keywords: *CCF, Thyroxin, Non-thyroidal illness syndrome.*

INTRODUCTION

Congestive cardiac failure is an important cause of mortality & morbidity. Despite modern therapeutic measures outcome has been notoriously bad. Effects of thyroxin on cardiac function in congestive cardiac failure have been a controversial subject. Advanced cardiac failure is associated with altered thyroid metabolism i.e. low serum T3 due to decreased serum conversion of T4 to T3.[1] This has previously been referred to as non-thyroidal illness syndrome.[2]

Initial studies emphasized the deleterious effect of thyroxin on the heart including the development of atrial fibrillation, exacerbation of angina pectoris and in rare cases heart failure as well. How ever recent work has shown beneficial effects of thyroid hormone on cardiovascular homodynamics. Moruzzi et.al. in their recent work has shown that this beneficial effect was maintained when thyroxin was given for 3 months with significant improvement on exercise performance ,cardiac contractility and circulatory parameters[3,4.]

A reduction in Lt. Ventricular diastolic dimension has been observed in the absence of ventricular remodeling (no change in left ventricular wall thickness and mass index) This effect is probably related to a long- standing reduction in peripheral vascular resistance and /or increase of cardiac contractility as suggested by the increase in left ventricular ejection fraction.[4]

Up till now no controlled study has been published in Pakistan. The present study has planned to observe the effect of the thyroxin in our patients of CCF. Thyroxin is a cheap drug and its addition is expected to be a cost effective way to improve therapeutic response.

MATERIAL AND METHODS

This was an interventional double blind placebo controlled clinical trial. The subjects were in two groups i.e. thyroxin group (cases) and placebo group (controls).

Characteristics of Thyroxin group (Cases) and Placebo group (Controls)

Subject variables	Cases (n=30)	Controls (n=30)
Age (years)	57.7 + 8.9	62 + 11.4
Men (%)	27%	56%
Pre-trial ejection fraction (%)	36.7 + 7.1	35.5 + 6.6
Post-trial ejection fraction (%)	41.3 + 7.9	36.2 + 7.7
Pre-trial cardio thoracic ratio (%)	60.7 + 8.3	59.4 + 8.1
Post-trial cardio thoracic ratio (%)	57.9 + 6.8	59.5 + 8.4
Pre-trial weight (kg)	63.4 + 14.7	63.8 + 15.4
Post-trial weight (kg)	64.13 + 14.8	63.5 + 14.8
Pre-trial NYHA Class (No of cases)		
I	0	0
II	12	16
III	18	10
IV	0	4
Post-trial NYHA Class (No of cases)		
I	0	0
II	17	17
III	13	11
IV	0	2
Pre-trial thyroid status (No of cases)		
Euthyroid	30	30
Hypothyroid	0	0
Hyperthyroid	0	0
Peri-trial thyroid status (No of cases)		
Euthyroid	30	30
Hypothyroid	0	0
Hyperthyroid	0	0
Post-trial thyroid status (No of cases)		
Euthyroid	30	30
Hypothyroid	0	0
Hyperthyroid	0	0

Table 1

Study population:

Pakistani subjects with congestive cardiac failure, visiting the medical and cardiology outpatient departments and those admitted in medical wards and coronary care unit of Fauji Foundation Hospital were enrolled in the study.

Sample size:

Experimental group of 30 cases and 30 controls were enrolled in the study.

Sampling Procedure:

Non-probability, convenience sampling. Subjects were chosen in the hospital setting.

Inclusion criteria

- Evidence of congestive cardiac failure (i.e. fulfilling the disease diagnostic criteria).
- Functionally the patient must be in NYHA Class II-IV.

Exclusion criteria

- Evidence of past or present thyroidal illness.
- Amiodarone therapy.
- Presence of arrhythmias.
- Patients of angina.
- Patients with structural lesions of heart.
- Pregnant and breast-feeding women.

Bar chart of Pre and Post-trial Ejection Fraction of Cases and Controls

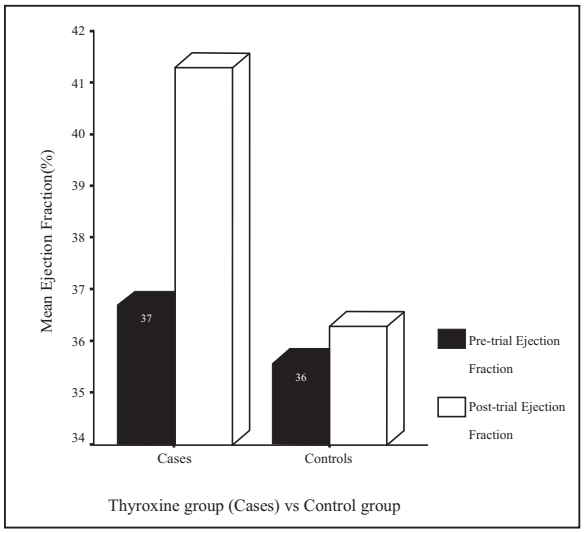

Figure- 1

Bar chart of Pre-trial NHYA Class of Cases and Controls

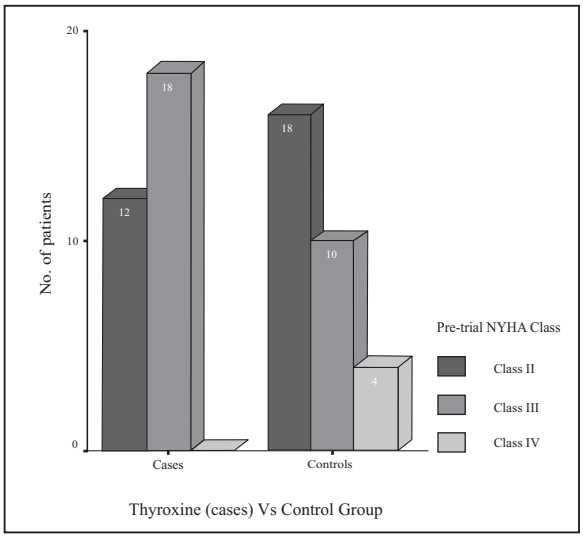

Figure- 2

- Patients with concomitant hypertension.
- Incomplete follow up.

DATA COLLECTION

1) Structured interview:

All subjects answered a questionnaire on their first visit, which included the following;

- Personal characteristics; name, age, sex, address, telephone number, and smoking habits.
- Evidence of heart failure and its severity.
- Past medical history of diabetes mellitus and hypertension.
- History of ischemic heart disease.
- Drugs being used by the patient.
- History of thyroid disease.

2) Physical measurements:

- Blood pressure was measured using a mercury sphygmomanometer
- Resting 12 lead electrocardiogram was obtained.
- Weight was measured.

Bar chart of Post-trial NYHA Class of Cases and Controls

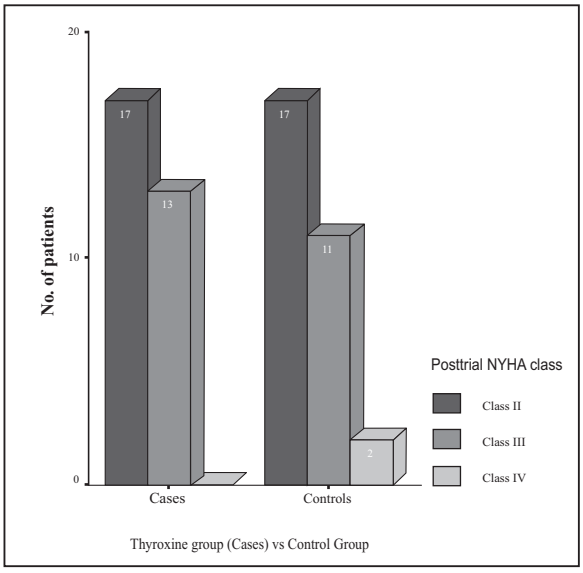

Figure- 3

Bar chart of Pre and Post-trial Cardio thoracic Ratio of Cases and Controls

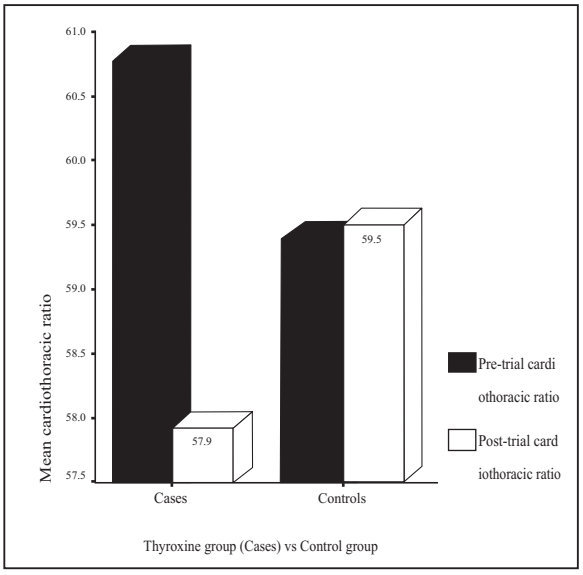

Figure- 4

Frequency Table of Ejection fraction of Thyroxin group (Cases)

Pre trial ejection fraction					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	20.00	1	3.3	3.3	3.3
	25.00	1	3.3	3.3	6.7
	26.00	1	3.3	3.3	10.0
	28.00	2	6.7	6.7	16.7
	29.00	1	3.3	3.3	20.0
	30.00	1	3.3	3.3	23.3
	31.00	1	3.3	3.3	26.7
	32.00	1	3.3	3.3	30.0
	34.00	1	3.3	3.3	33.3
	35.00	3	10.0	10.0	43.3
	36.00	2	6.7	6.7	50.0
	38.00	1	3.3	3.3	53.3
	40.00	2	6.7	6.7	60.0
	41.00	1	3.3	3.3	63.3
	43.00	6	20.0	20.0	83.3
	44.00	2	6.7	6.7	90.0
	45.00	2	6.7	6.7	96.7
	46.00	1	3.3	3.3	100.0
	Total	30	100.0	100.0	

STATISTICAL ANALYSIS

The whole data of this study was stored and statistically analyzed using the Statistical Package for Social Sciences (SPSS). The data about pre and post-trial ejection fraction of cases and controls were summarized in frequency distribution tables and were presented using the bar charts. Measure of central tendency i.e. mean, was calculated for both groups. The dispersion of results was presented as range and standard deviation. The data about pre and post-trial cardio-thoracic ratios, weight and NYHA class were also presented using the bar charts. To determine the difference between mean Pre and Post-trial ejection fractions of cases and controls, Paired-Samples t test was used. $P < 0.05$ was considered statistically significant.

RESULTS

In Table 1 we present the characteristics of the two groups.

All the patients were eurthyroid at the start of study and remained euthyroid, till the end of study period according to results of serum TSH. T3, T4 levels. In thyroxin group 5 patients improved from NYHA Class III to NYHA Class II. On the other hand in control group two patients improved from NYHA Class IV to NYHA Class II and III respectively.

The mean ejection fraction improved from 36.77.1 to 41.37.9 in thyroxin group. There was a smaller improvement from 35.56.6 to 36.27.7 in ejection fraction of control group. The mean cardio-thoracic ratio reduced from 60.78.3 to 57.96.8 after treatment with thyroxin. There was no change in Cardio thoracic ratio at the end of study period in control group (59.48.1 and 59.58.4 respectively).

There was no change noted in weight of both groups at the end of study period. No patient developed any rhythm disturbance during treatment with thyroxin.

To test the null hypothesis that the mean ejection fraction of patients with congestive cardiac failure did not change after receiving thyroxin for 3 months

i.e.; $\mu_{\text{Pre-trial ejection fraction of cases}} = \mu_{\text{Post-trial ejection fraction of cases}}$,

we used the results of Paired-Samples t-test.

The Paired-Samples T Test procedure compares the means of two variables that represent the same group at different times (e.g. before and after an event). The mean values for the two variables are displayed in the Paired Samples Statistics Tablesee Table 6 6 low significance value for the t test (typically less than 0.05) indicates that there is a significant difference between the two variables. If the confidence interval for the

Frequency Table of Ejection fraction of Thyroxin group (Cases)

Pre trial ejection fraction					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	24.00	1	3.3	3.3	3.3
	30.00	2	6.7	6.7	10.0
	31.00	1	3.3	3.3	13.3
	32.00	1	3.3	3.3	16.7
	33.00	1	3.3	3.3	20.0
	35.00	2	6.7	6.7	26.7
	37.00	1	3.3	3.3	30.0
	38.00	1	3.3	3.3	33.3
	40.00	4	13.3	13.3	46.7
	42.00	4	13.3	13.3	60.0
	45.00	4	13.3	13.3	73.3
	47.00	3	10.0	10.0	83.3
	48.00	1	3.3	3.3	86.7
	50.00	1	3.3	3.3	90.0
	55.00	2	6.7	6.7	96.7
	57.00	1	3.3	3.3	100.0
	Total	30	100.0	100.0	

Table 2

mean difference does not contain zero, this also indicates that the difference is significant.

Since the observed significance level for the test is 0.00, which is less than 0.05, we can reject the hypothesis that the variances of two groups are equal.

The mean ejection fraction of the two groups differs by -4.6%; with standard error of the mean difference of 0.89. The computed t-statistic (which tells us how many standard errors units from the population mean difference of 0 the observed difference falls) is -5.14.

The observed two-tailed significance level is 0.00, which means that there is a 0% chance to see a sample difference of 4.6 if the null hypothesis is correct and the population means are equal. In other words, the probability of committing type I error (i.e. wrongly rejecting the H_o which is true) is 0%. Since 0.00 is less than 0.05 we reject the null hypothesis that the two groups of subjects had equal Pre and Post-trial ejection fractions and the observed results are unusual if the null hypothesis is true.

The 95% confidence interval for the true difference is from –6.4 to –2.7. This means that it is likely that the true mean difference is any where between these values.

Therefore, we found statistically significant difference between the mean Pre and Post-trial ejection fractions of those patients of congestive cardiac failure who received thyroxin for 3 months and this difference is unlikely to be due to chance.

To test the null hypothesis that the mean ejection fraction of patients with congestive cardiac failure did not change after receiving placebo for 3 months.

i.e.; $\mu_{\text{Pre-trial ejection fraction of controls}} = \mu_{\text{Post-trial ejection fraction of controls}}$

we again applied the Paired-Samples t-test. the observed significance level for the test is 0.517, which is more than 0.05 we can accept the hypothesis.

The mean ejection fraction of the two groups differs by – 0.7%; with standard error of the mean difference of 1.06. The computed t-statistic is –0.656. The 95% confidence interval for the true difference is from –2.88 to 1.48.

Therefore, we found no statistically significant difference between the mean Pre and Post-trial ejection fractions of those patients of congestive cardiac failure who received placebo for 3 months.

Similar reduction of mean Cardio thoracic ratio of 2.83 was observed after treatment with thyroxin. This was statistically significant (p = 0.041). Such improvement in cardio thoracic ratio was not observed in placebo group (p =0.907).

Descriptive Statistics Of Ejection Fraction of Thyroxin Group (Cases)

Statistics			
		Pre trial ejection fraction	Post trial ejection fraction
N	Valid	30	30
	Missing	0	0
Mean		36.7000	41.3000
Std. Error of Mean		1.2991	1.4497
Median		37.0000	42.0000
Mode		43.00	40.00(a)
Std. Deviation		7.1155	7.9401
Variance		50.6310	63.0448
Range		26.00	33.00
Minimum		20.00	24.00
Maximum		46.00	57.00
Percentiles	25	30.7500	35.0000
	50	37.0000	42.0000
	75	43.0000	47.0000
	95	45.4500	55.9000
a Multiple modes exist. The smallest value is shown			

Table 3

DISCUSSION

The important findings of our study were that the mean ejection fraction of Thyroxin group improved by 4.6%. This difference between mean pre and post-trial ejection fraction is statistically significant (P= .000). There was also a statistically significant reduction in cardio-thoracic ratio in this group.

On the other hand, the mean ejection fraction of Placebo group changed by 0.7%. This difference is not statistically significant (p 0.517). There was also no statistically significant reduction in cardio-thoracic ratio in this group (p 0.907). There was similar significant reduction in cardio-thoracic ratio after treatment with thyroxin. In thyroxin group 5 patients improved from NYHA Class III to NYHA Class II. On the other hand in control group two patients improved from NYHA Class IV to NYHA Class II and III respectively. This improvement and the slight reduction in ejection fraction seen in placebo group might be due to better compliance with medications in patients registered for study as compared to general population.

Thyroxin was well tolerated and no patients developed chemical hyperthyroidism since thyroxin and thyroid-stimulating hormone plasma levels remained within normal limits.

There was no change in mean weight in both groups at the end of study period.

The results of ECG at every follow-up visit were encouraging as no rhythm disturbances were noted which would have mandated the use of Holter monitoring. The absence of significant arrhythmias might be explained by the improvement of cardiac function and activation of sodium –calcium pumps by thyroxin in heart failure in which alterations in intracellular calcium homeostasis might be important in generating arrhythmias.

It has long been recognized that thyroid hormone exerts effects on the heart and systemic circulation.[5] Whereas initial studies emphasized the deleterious effect of thyroid disease including the development of atrial fibrillation, exacerbation of angina pectoris and in rare cases heart failure, recent work has demonstrated the beneficial effects of thyroid hormone on cardiovascular hemodynamics[3, 4]

In both humans and experimental animals thyroid hormone has been shown to increase cardiac inotropy and to lower the systemic vascular resistance [6,7,8,9,10]

It is well documented that patients with advanced heart failure, after coronary artery bypass surgery and after myocardial infarction, have altered thyroid hormone metabolism with low serum triidothyronine (T3) levels.[1] This occurs mainly as the result of decrease in the conversion of T4 to T3.This has been referred to as low T3 or nonthyroidal illness syndrome.[3]

Thus, coupling the potential benefits of

Paired Samples T-Test for Cases for comparing mean Pre and Post-trial Ejection Fractions

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre trial ejection fraction	36.7000	30	7.1155	1.2991
	Post trial ejection fraction	41.3000	30	7.9401	1.4497

Paired Samples Correlations				
		N	Correlation	Sig
Pair 1	Pre trial ejection fraction & Post trial ejection fraction of cases	30	.794	.000

thyroid hormone to enhance cardiac performance with the inherently low serum levels of T3, a heart failure treatment regimen that includes thyroid hormone replacement in a carefully monitored setting seems rational. Lingering concerns for adverse effects of thyroid hormone on cardiac oxygen consumption and rhythm disturbances, however, has tempered enthusiasm for its use despite multiple reports showing the safety of short and intermediate-term thyroid hormone treatment in various models of heart disease.

Hamilton and colleagues in 1996 studied the safety and hemodynamic effectiveness of T3 administration to patients with advanced heart failure. Their clinical observations were quite remarkable. The T3-treated patients showed no evidence of rhythm disturbance, clinical signs if ischemia or change in metabolic rate. A significant increase in cardiac output was recorded in 45% of all patients. These data are similar to those reported by Klemperer et al, for high risk patients undergoing coronary artery bypass grafting. In this study there was a postoperative increase in cardiac output and a decrease in systemic vascular resistance recorded in T3-reated patients compared with results in a randomized placebo control group. Improved cardiac performance was also reported by Moruzzi and colleagues in a long term study of oral thyroid hormone treatment of patients with dilated cardiomyopathy.

The interest in thryroxine therapy in cardiac failure is still a topic of interest and its efficacy and safety being assessed by various researchers. Recently pantos et al has opined that changes in thyroid hormone were closely correlated to myocardial functional status in

Paired Samples Test									
		Paired Differences							
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		t	df	Sig. (2-tailed)
					Lower	Upper			
Pair 1	Pre trial ejection fraction - Post trial ejection fraction of cases	-4.6000	4.8962	.8939	-6.4283	-2.7717	-5.146	29	.000

Table 4

Frequency Table of ejection Fraction of Placebo Group (Controls)

Post trial ejection fraction					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	20.00	1	3.3	3.3	3.3
	22.00	1	3.3	3.3	6.7
	23.00	1	3.3	3.3	10.0
	28.00	1	3.3	3.3	13.3
	30.00	2	6.7	6.7	20.0
	31.00	3	10.0	10.0	30.0
	34.00	3	10.0	10.0	40.0
	35.00	4	13.3	13.3	53.3
	38.00	2	6.7	6.7	60.0
	39.00	1	3.3	3.3	63.3
	40.00	4	13.3	13.3	76.7
	42.00	1	3.3	3.3	80.0
	45.00	2	6.7	6.7	86.7
	46.00	1	3.3	3.3	90.0
	47.00	1	3.3	3.3	93.3
	48.00	1	3.3	3.3	96.7
	52.00	1	3.3	3.3	100.0
	Total	30	100.0	100.0	

patients with heart failure. These data probably indicate a possible role of thyroid hormone in the pathophysiology of heart failure and confirm previous experiments[12]. Similarly in another article by Pingitos et al it was concluded that the administration of synthetic triiodothyronine (T(3)) was well tolerated and induced significant improvement in cardiac function without increased heart rate and metabolic demand. The author suggested large multicenter, placebo-controlled prospective studies are to evaluate the safety and prognostic effects of chronic treatment with TH replacement therapy in patients with heart failure[13].

Our study had many limitations. The improvement in ejection fraction may only be due to the better compliance of study population with medications as compared to general population. This error could have been minimized by stabilizing patients on regular anti-failure medication for three months before entering them into the study. Our sampling was not random. Appropriate matching did not control age and sex distribution of patients. A further problem was the small sample size. The study duration was only three months and we did not study long term effects of thyroxin in heart failure. Moreover, the main outcome measure was measurement of ejection fraction, which is observer dependant and the method used was 2-D M-mode estimations of fractional shortening and volume changes. These are less accurate as compared to 3-D echocardiographic volume scans. Similarly other measures of cardiac performance like cardiopulmonary exercise test and hemodynamic evaluation of cardiac output, myocardial oxygen demand and systemic vascular resistance were not used in our study. Holter monitoring was done only in those patients who had any evidence of rhythm disturbance on ECG, rather than doing it routinely for all patients at the start and end of study period. Our study was obviously too limited to address the issue of mortality. These limitations can lead to spurious associations and to inflated estimations of the strength of any real association.

CONCLUSION

We conclude that in heart failure a three month treatment with thyroxin has beneficial effects in terms of increasing the ejection fraction of the failing heart without inducing undesired effects like rhythm disturbances.

However, to make thyroxin a part of routine prescription of patients of heart failure, more studies are required to demonstrate the beneficial effect beyond reasonable doubt and to remove the concerns regarding its effect on increasing myocardial oxygen demand and rhythm disturbances.

Similarly, this opens new channels for investigating other similar novel metabolic substances like growth hormone in treatment of

Pre trial ejection fraction					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	21.00	1	3.3	3.3	3.3
	24.00	1	3.3	3.3	6.7
	25.00	1	3.3	3.3	10.0
	28.00	1	3.3	3.3	13.3
	30.00	4	13.3	13.3	26.7
	31.00	1	3.3	3.3	30.0
	32.00	1	3.3	3.3	33.3
	35.00	5	16.7	16.7	50.0
	36.00	1	3.3	3.3	53.3
	37.00	3	10.0	10.0	63.3
	38.00	1	3.3	3.3	66.7
	39.00	1	3.3	3.3	70.0
	40.00	4	13.3	13.3	83.3
	42.00	1	3.3	3.3	86.7
	43.00	1	3.3	3.3	90.0
	46.00	1	3.3	3.3	93.3
	48.00	2	6.7	6.7	100.0
	Total	30	100.0	100.0	

heart failure. Attempts can be made to develop thyroid hormone analogs to maximize the positive inotropic effects while minimizing the unwanted effects of hormone on bone, skeletal muscle and heart rate.

As with all new therapies, a vigilant approach needs to be maintained until we have expanded our understanding of this novel and potentially useful treatment modality.

REFERENCES

1- Hamilton MA, Stevenson LW, Luu M. Walden

Descriptive Statistics for Ejection Fraction of Placebo Group (Controls)

Descriptive Statistics			
		Pre trial ejection fraction	Post trial ejection fraction
N	Valid	30	30
	Missing	0	0
Mean		36.2667	35.5667
Std. Error of Mean		1.4166	1.2183
Median		35.0000	35.5000
Mode		35.00(a)	35.00
Std. Deviation		7.7590	6.6731
Variance		60.2023	44.5299
Range		32.00	27.00
Minimum		20.00	21.00
Maximum		52.00	48.00
Percentiles	25	31.0000	30.0000
	50	35.0000	35.5000
	75	40.5000	40.0000
	95	49.8000	48.0000
a Multiple modes exist. The smallest value is shown			

Table 5

Paired-Samples t-test for Controls for comparing mean Pre and Post-trial Ejection Fractions

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre trial ejection fraction of controls	35.5667	30	6.6731	1.2183
	Post trial ejection fraction of controls	36.2667	30	7.7590	1.4166

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	Pre trial ejection fraction & Post trial ejection fraction of controls	30	.682	.000

JA. Altered thyroid hormone metabolism in advanced heart failure. J Am Coll Cardiol 1990;16:91-95

2- Utiger RD. Altered thyroid function in nonthyroidal illness and surgery: to treat or not to treat. N Engl j Med. 1994;333:1562-3

3- Morruzi P. Doria E, Agostini PG. Medium term effectiveness of l-thyroxine treatment in idiopathic dilated cardiomyopathy . Am j Med 1996;101:461-7

4- Klemperer, JDKlein I, Gomez M, Helm RE, Ojamaa K, Thomas SJ, Isom OW , Krieger K. Effect of thyroid hormone supplementation in cardiac surgery .N Engl J Med 1995;333:1622-7

5- Polikar R, Burger AG, Scherrer U, et al. The thyroid and the heart. Circulation 1993; 87:1435-41

6- Ojamaa K, Klemperer JD, Klein I. Acute effects of thyroid hormone on vascular smooth muscle. Thyroid 1996; 6: 505-1

7- Ojamaa K, Sabet A, Kenessey A, Shenoy R, Klein I. Regulation of rat cardiac Kv1.5 gene expression by thyroid hormone is rapid and chamber specific. Endocrinology 1999; 140: 3170-6

8- Ojamaa K, Klemperer JD, MacGilvray SS, Klein I, Samarel A. Thyroid hormone and hemodynamic regulation of beta-myosin heavy chain promoter in the heart. Endocrinology 1996;137:802-8

9- Ojamaa K, Klein I, Sabet A, Steinberg SF. Changes in adenyl cyclase isoforms as a mechanism for thyroid hormone modulation of

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre trial ejection fraction - Post trial ejection fraction of Controls	-.7000	5.8437	1.0669	-2.8821	1.4821	-.656	29	.517

Table 6

cardiac beta-adrenergic receptor responsiveness. Metabolism 2000;49:275-9

10- Klein I, Ojamaa K. Thyroid hormone treatment of congestive heart failure. Am J Cardiol 1998;81:490-

11- Klemperer J, Ojamaa K, Klein I. Thyroid hormone therapy in cardiovascular disease. Prog Cardiovasc Dis 1996;38:329-36.

12- Pantos C, Dritsas A, Mourouzis I, Dimopoulos A, Karatasakis G, Athanassopoulos G, Mavrogeni S, Manginas A, Cokkinos DV. Eur J Endocrinol. 2007;157(4):515-20.

13- Pingitore A, Tervasi G. Recent Patents Cardiovasc Drug Discov. 2008;3(1):19-27

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