Endocrinology & Metabolic Syndrome

Cokkinos and Chryssanthopoulos, Endocrinol Metab Syndr 2016, 5:4
DOI: 10.4172/2161-1017.1000246

Commentary Open Access

Thyroid Hormones and the Heart; a Paradigm of Exquisite Fine Tuning, Combining Ancient Hellenic and Oriental Wisdom

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Received date: July 15, 2016; **Accepted date:** July 20, 2016; **Published date:** August 04, 2016

Commentary

We have previously summarized evidence [1-3] the thyroid hormones (TH) can diminish left ventricular (LV) remodeling (REM) after an acute myocardial infarction (AMI). Experimental animal data were mostly given but also some results from studies in humans.

It must be realized that REM, very plainly defined as LV cavity enlargement above a certain value remains an important cardiological problem. After an anterior AMI despite early primary percutaneous intervention (PPCI) and administration of the drugs considered most efficient today, i.e. Converting enzyme inhibitors (CEIs) or angiotensin receptor blockers (ARBs), β- blockers and aldosterone inhibitors, 30% of patients (pts) develop REM which seriously undermines their survival [4].

Apart from the aforementioned drugs, a legion of substances has given excellent results in the animal, but has had only limited success in the human [3].

Thus, a drug that can effectively reduce REM without significant side effects, is still needed.

Before embarking on enthusiastic employment of thyroid hormones (TH) in the post infarct heart, an all-important caveat concerning previous studies should be remembered:

Many author groups including our own, have found that TH administration improves the course towards REM by multiple pathways, i.e. inhibition of apoptosis, reduction of collagen accumulation increase of contractility as effected by SERCA-2α, αMHC and β1 adrenergic receptor up-regulation, induction of cardioprotective mechanisms including Akt , ERK 1/2 and mitochondrial biogenesis [3,5-8].

However, an established fact remains that although hypothyroidism correction is beneficial and that early TH administration can improve cardiac function, there is no escaping the fact prolonged that TH in high doses becomes detrimental to the heart, leading to hypertrophy and heart failure (HF) [9,10].

There is an analogy in this course to this of “compensatory” or “adaptive” H after an acute myocardial infarction (AMI). The transition between this it and “pathological” or “maladaptive” is practically impossible to define [11].

The TH actions can very well be explained by the yin and yang theory of ancient Tao Philosophy in which every state has its positive and opposite side, and the “nothing in excess” and “all evil is associated with (some) good” of Ancient Hellenic Philosophy.

Some Paradigms Should be Given

Most studies have shown that TH administration initially increases +dp/dt, -dp/dt, and SV. However, Maity et al. [12] have shown that after 5-8 days in the rat these begin to diminish. Heart failure in hyperthyroidism is well known, even without atrial fibrillation and disproportionate tachycardia. TH promote mitochondrial (MITO) genesis through a genomic action [13]. Cardiomyocytes have the highest volume of MITO (30%), of all cells according to Maity et al. [12], who have shown that TH eventually diminish the mitochondrial membrane proteins prohibitin and VDAC, suggesting a noxious action on the mitochondria.

Also, it is well known that TH can increase angiogenesis [14]. However what happens when too much H ensues after their prolonged administration has not been well studied.

Most authors have shown that TH increases tissue oxidation. This process up to a point can be quite beneficial, since it increases HSP70 expression; actually (MDA) is involved in ischemic preconditioning according to Downey et al. [15]. Obviously it is a question of time and dosage. Maity et al. [12] showed that T3 causes < more than 2 fold increase of lipid peroxidation. De Sibio et al. [16] also found that in rats T3 at higher doses causes tissue oxidative stress and genotoxicity.

Another important aspect of TH administration is increased energy consumption. Obviously, this should be offset by commensurate energy production. TH has been proposed as increasing glucose oxidation [17] and even increase FAO in aged mice [18].

However, Queiroz et al. [19] have shown that T3 treatment decreased the total Cr content and CrP, Cr, CrP/Cr and ATP, the main fuels of the myocardium.

Additionally, Maity et al. [12] showed that ATP is increased very early (day 2) in the rat decreasing progressively from day 5 to 15. The rats received 8 μg/100 μg BW ip for 15 days. These authors stressed that as ATP levels keep decreasing, the inotropic effects of SERCA-2 are annulled.

Matoba [20] based on the findings of Kajimoto et al. [21] that triiodothyronine activates lactate oxidation without impairing fatty acid oxidation and improves weaning from extracorporeal membrane oxygenation, proposes T3 administration as therapy for cardiac metabolism in the failing heart. It should be noted that Kajimoto et al. [21] gave T3 for about 8 hours.

The “nothing in excess" adage is very pertinently pictured by our finding [22] that Akt, a determining factor for the expression of psychological H, becomes deleterious when overexpressed due to high T3 doses . Accordingly, Matsui et al. [23], have also shown that transgenic rats overexpressing Akt develop myocardial fibrosis.

Three additional activities by which TH can hinder REM all of the following:

Continuous conditioning

Wei et al. [24] have shown that in the rat, conditioning applied one week after an experimental AMI can diminish REM as measured at 1 month. Currently, three studies applying a remote conditioning after an AMI in the human are under way. We have shown that TH can protect the heart in preconditioning- like way [25]. Thus, it can be postulated that their continued administration can effect prolonged myocardial preservation.

Stimulation of regeneration

As the questions surrounding the mechanisms of action and effectiveness of progenitor cell therapy remains unanswered; a new concept is gaining ground: that of enhancing endogenous regenerative activity [26]. In this field TH are showing promise.

One of the authors (DVC) has been long interested in the possible regeneration –apart from the cardioprotective-effects of thyroid hormones [27]. Naqvi et al. [28] showed that a thyroid hormone surge at postnatal day -15 in mice activates the IGF-1/IGF-1-R/ Akt pathway and initiates a brief but intense proliferative burst of predominantly binuclear cardiomyocytes increasing their number by ≈40%; when T3 biosynthesis is inhibited, cardiomyocyte numbers are reduced.

An additional aspect is the effect of TH on the pluripotent stem cell themselves. Thus, Yang et al. [29] have shown that T3 promotes the modulation of human cardiomyocytes derived from induced pluripotent stem cells.

Reduction of inflammation

There is increasing evidence that the index AMI can stimulate innate immunity which further endangers Cell Death and REM. TH may favorably influence innate immunity and natural killing activity [30-33]. This is a rapidly expanding field.

The practical questions of TH administration

Coming to more practical considerations, is clinical TH administration a viable option after an AMI? As already discussed, apart from the "big 3" no other drug has proven effective against REM in the clinical context. It is understandable that whichever drug is considered, it should be administrated in conjunction with these 3 drug families. The same pertains to TH. Additionally, if these drugs produce oxygen-wasting tachycardia, adequate β-blocker dosage with addition of ivabradine if necessary [34], should be considered. RAS antagonism and β-blockade may prevent H development as we have shown [35,36]. However, Gerdes et al. [9] found that propranolol does mitigate the noxious effects of TH induced H.

In animals we have shown that dosage is important: Greater doses of T3 after old infarcts were beneficial [37] however in early post-infarct rats they actually caused greater REM and CHF, associated with an overt increase of Akt, as already mentioned [22]. Ojamaa et al. [38] in rats found that only higher doses (20 mg/day) increased SERCA-2α and SERCA-2α/PLB ratio and αMHC.

However most authors recommend lower doses in clinical practice [39].

Another important question is to which patients should TH be administered. Possibly only in larger infarcts which may present a course towards REM. The prognostic value of various imaging and marker measurements is beyond the scope of this commentary. However, an important biomarker should not be overlooked: Many authors have shown that a low fT3 or T3 after an AMI is strongly prognostic of a worse course [40] and a course towards REM [41]. Thus, actually Iervasi et al. [42] gave liiodothyronine only to patients after an acute MI with low serum T3 levels. They tried to bring these levels to not higher than normal. They showed a modest Improvement in cardiac structure and function, without any appreciable adverse effects. The THiRST study is part of a large PONTE study. Further results, and those of the study by Jabbar et al. [43] are eagerly awaited.

Conclusions - Future Directions

TH administration after a large AMI in patients with low serum T3 or fT3 levels is a plausible addition to the already widely used drug families, i.e. ACEi, ARBs, β-blockers and aldosterone antagonists. T3 maybe the formulation of choice. The exact dosage and duration of therapy remain to be determined. However smaller doses according to the "nothing in excess" adage would appear preferable, rendering this treatment safe and well-tolerated. Hopefully it may be added to the limited arsenal of anti-REM therapies.

This commentary is necessarily limited; we did not include less clinically relevant aspects, such as fibrosis, and microRNA expression changes. Obviously this is a rapidly changing subject.

References

1. Pantos C, Mourouzis I, Markakis K, Dimopoulos A, Xinaris C, et al. (2007) Thyroid hormone attenuates cardiac remodeling and improves hemodynamics early after acute myocardial infarction in rats. Eur J Cardiol Thorac Surg 32: 333-339.
2. Pantos C, Mourouzis I, Markakis K, Tsagoulis N, Panagiotou M, et al. (2008) Long-term thyroid hormone administration reshapes left ventricular chamber and improves cardiac function after myocardial infarction in rats. Basic Res Cardiol 103: 308-318.
3. Cokkinos DV, Chryssanthopoulos S (2016) Thyroid hormones and cardiac remodeling. Heart Fail Rev 21: 365-372.
4. Tardif JC, O'Meara E, Komajda M, Böhm M, Borer JS, et al. (2011) Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. Eur Heart J 32: 2507-2515.
5. Pantos C, Mourouzis I, Saranteas, Clavé G, Ligeret H, et al. (2009) Thyroid hormone improves postischaemic recovery of function while limiting apoptosis: a new therapeutic approach to support hemodynamics in the setting of ischaemia–reperfusion? Basic Research in Cardiol 104: 69-77.
6. Chen YF, Kobayashi S, Chen J, Redetzke RA, Said S, et al. (2008) Short term triiodo-L-thyronine treatment inhibits cardiac myocyte apoptosis in border area after myocardial infarction in rats. J Mol Cell Cardiol 44: 180-187.
7. Verga Falzacappa C, Timperi E, Bucci B, Amendola D, Piergrossi P, et al. (2012) T(3) preserves ovarian granulosa cells from chemotherapy-induced apoptosis. J Endocrinol 215: 281-289.
8. Cokkinos DV, Pantos C (2009) Thyroid hormones and their action on the myocardium. Bull Acad Natl Med 193: 327-336.
9. Gerdes AM, Moore JA, Bishop SP (1985) Failure of propranolol to prevent chronic hyperthyroid induced cardiac hypertrophy and multifocal cellular necrosis in the rat. Can J Cardiol 1: 340-345.
10. Degens H, Gilde AJ, Lindhout M, Willemsen PH, Van Der Vusse GJ, et al. (2003) Functional and metabolic adaptation of the heart to prolonged

thyroid hormone treatment. Am J Physiol Heart Circ Physiol 284: H108-H115.

11. Hill JA, Olson EN (2008) Cardiac plasticity. N Engl J Med 358: 1370-1380.
12. Maity S, Kar D, De K, Chander V, Bandyopadhyay A (2013) Hyperthyroidism causes cardiac dysfunction by mitochondrial impairment and energy depletion. J Endocrinol 217: 215-228.
13. Goglia F, Moreno M, Lanni A (1999) Action of thyroid hormones at the cellular level: the mitochondrial target. FEBS Lett 452: 115-120.
14. Tomanek RJ, Zimmerman MB, Suvarna PR, Morkin E, Pennock GD, et al. (1998) A thyroid hormone analog stimulates angiogenesis in the post-infarcted rat heart. J Mol Cell Cardiol 30: 923-932.
15. Downey JM, Davis AM, Cohen MV (2007) Signaling pathways in ischemic preconditioning. Heart Fail Rev 12: 181-188.
16. De Sibio MT, Luvizotto RA, Olimpio RM, Corrêa CR, Marino J, et al. (2013) A comparative genotoxicity study of a supraphysiological dose of triiodothyronine (T3) in obese rats subjected to either calorie-restricted diet or hyperthyroidism. PLoS One 8: e56913.
17. Rajagopalan V, Gerdes AM (2015) Role of thyroid hormones in ventricular remodeling. Curr Heart Fail Rep 12: 141-149.
18. Ledee D, Portman MA, Kajimoto M, Isern N, Olson AK (2013) Thyroid hormone reverses aging-induced myocardial fatty acid oxidation defects and improves the response to acutely increased afterload. PLoS One 8: e65532.
19. Queiroz MS, Shao Y, Berkich DA, Lanoue KF, Ismail-Beigi F (2002) Thyroid hormone regulation of cardiac bioenergetics: role of intracellular creatine. Am J Physiol Heart Circ Physiol 283: H2527-H2533.
20. Matoba S (2014) Triiodothyronine as a therapeutic candidate for cardiac metabolism in the failing heart. Circ J 78: 2836-2837.
21. Kajimoto M, Levee DR, Xu C, Kajimoto H, Isern NG, et al. (2014) Triiodothyronine activates lactate oxidation without impairing fatty acid oxidation and improves weaning from extracorporeal membrane oxygenation. Circ J 78: 2867-2875.
22. Mourouzis I, Mantzouratou P, Galanopoulos G, Kostakou E, Roukounakis N, et al. (2012) Dose-dependent effects of thyroid hormone on post-ischemic cardiac performance: potential involvement of Akt and ERK signalings. Mol Cell Biochem 363: 235-243.
23. Matsui T, Li L, Wu JC, Cook SA, Nagoshi T, et al. (2002) Phenotypic spectrum caused by transgenic overexpression of activated Akt in the heart. J Biol Chem 277: 22896-22901.
24. Wei M, Xin P, Li S, Tao J, Li Y, et al. (2011) Repeated remote ischemic postconditioning protects against adverse left ventricular remodeling and improves survival in a rat model of myocardial infarction. Circ Res 108: 1220-1225.
25. Pantos CI, Malliopoulou VA, Mourouzis IS, Karamanoli EP, Paizis IA, et al. (2002) Long-term thyroxine administration protects the heart in a pattern similar to ischemic preconditioning. Thyroid 12: 325-329.
26. Ali SR, Hippenmeyer S, Saadat LV, Luo L, Weissman IL, et al. (2014) Existing cardiomyocytes generate cardiomyocytes at a low rate after birth in mice. Proc Natl Acad Sci USA 111: 8850-8855.
27. Pantos C, Mourouzis I, Cokkinos DV (2012) Thyroid hormone and cardiac repair/regeneration: from Prometheus myth to reality? Can J Physiol Pharmacol 90: 977-987.
28. Naqvi N, Li M, Calvert JW, Tejada T, Lambert JP, et al. (2014) A proliferative burst during preadolescence establishes the final cardiomyocyte number. Cell 157: 795-807.
29. Yang X, Rodriguez M, Pabon L, Fischer KA, Reinecke H, et al. (2014) Tri-iodo-l-thyronine promotes the maturation of human cardiomyocytes-derived from induced pluripotent stem cells. J Mol Cell Cardiol 72: 296-304.
30. Mariani E, Ravaglia G, Forti P, Meneghetti A, Tarozzi A, et al. (1999) Vitamin D, thyroid hormones and muscle mass influence natural killer (NK) innate immunity in healthy nonagenarians and centenarians. Clin Exp Immunol 116: 19-27.
31. Kmiec Z, Myśliwska J, Rachón D, Kotlarz G, Sworczak K, et al. (2001) Natural killer activity and thyroid hormone levels in young and elderly persons. Gerontol 47: 282-288.
32. Hodkinson CF, Simpson EE, Beattie JH, O'Connor JM, Campbell DJ, et al. (2009) Preliminary evidence of immune function modulation by thyroid hormones in healthy men and women aged 55-70 years. J Endocrinol 202: 55-63.
33. De Vito P, Balducci V, Leone S, Percario Z, Mangino G, et al. (2012) Nongenomic effects of thyroid hormones on the immune system cells: New targets, old players. Steroids 77: 988-995.
34. Kim BH, Cho KI, Kim SM, Kim N, Han J, et al. (2013) Heart rate reduction with ivabradine prevents thyroid hormone-induced cardiac remodeling in rat. Heart Vessels 28: 524-535.
35. Pantos CI, Mourouzis IS, Tzeis SM, Malliopoulou V, Cokkinos DD, et al. (2000) Propranolol diminishes cardiac hypertrophy but does not abolish acceleration of the ischemic contracture in hyperthyroid hearts. J Cardiovasc Pharmacol 36: 384-389.
36. Pantos C, Paizis I, Mourouzis I, Moraitis P, Tzeis S, et al. (2005) Blockade of angiotensin II type 1 receptor diminishes cardiac hypertrophy, but does not abolish thyroxin-induced preconditioning. Horm Metab Res 37: 500-504.
37. Pantos C, Mourouzis I, Tsagoulis N, Markakis K, Galanopoulos G, et al. (2009) Thyroid hormone at supra-physiological dose optimizes cardiac geometry and improves cardiac function in rats with old myocardial infarction. J Physiol Pharmacol 60: 49-56.
38. Ojamaa K, Kenessey A, Shenoy R, Klein I (2000) Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. Am J Physiol 279: E1319-E1324.
39. Weltman NY, Ojamaa K, Savinova OV, Chen YF, Schlenker EH, et al. (2013) Restoration of cardiac tissue thyroid hormone status in experimental hypothyroidism: a dose-response study in female rats. Endocrinology 154: 2542-2552.
40. Friberg L, Werner S, Eggertsen G, Ahnve S (2002) Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina? Archives of Internal Medicine 162: 1388-1394.
41. Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, et al. (2011) Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association? European J Endocrinol 165: 107-114.
42. Iervasi G (2012) THiRST: Thyroid Hormone Replacement therapy in ST elevation myocardial infarction (The PONTE pilot study). Cambridge University.
43. Jabbar A, Ingoe L, Pearce S, Zaman A, Razvi S (2015) Thyroxine in acute myocardial infarction (ThyrAMI): levothyroxine in subclinical hypothyroidism post-acute myocardial infarction: study protocol for a randomised controlled trial. Trials 16: 115.