# Hypothyroidism and the Heart: Much More Than Meets the Eye

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The pleiotropic effects of thyroid hormone are essential from the embryonic state for the optimal development, maturation, and functioning of cardiac tissue. In addition, thyroid hormone (TH) has been shown to play a critical reparative role in the setting of myocardial injury.[1] Hypothyroidism is associated with hyperlipidemia, an increased risk of coronary artery disease, and left ventricular systolic and diastolic dysfunction.[1] In issue 13.2 of this journal, Udovcic et al. presented a clinically relevant and concise review titled "Hypothyroidism and the Heart."[2] Even so, several key aspects of the interaction between TH and heart disease deserve attention—specifically, the complex biological mechanisms underlying the role of TH in the development of heart failure.

Abnormal thyroid function can affect cardiac metabolism, structure, function, and response to therapy. In a hypothyroid state, cardiac tissue shows poor substrate utilization (glucose, lactate, and free fatty acids) by mitochondria. Hypothyroidism stimulates fibroblasts and promotes myocardial fibrosis and, eventually, cardiac dysfunction.[3] In adult rats, long-standing hypothyroidism has been shown to cause loss of coronary arterioles and a maladaptive change in myocyte shape that eventually lead to the development of heart failure.[4] Alterations in TH receptor homeostasis are shown to regulate regression of the damaged myocardium to the fetal phenotype. Thyroid hormone treatment may preferentially rebuild the injured myocardium by reactivating developmental gene programming and fetal phenotype, leading to cell dedifferentiation and creating a permissive state for regeneration.[5]

Cross-sectional studies have demonstrated low levels of T3 in about 30% of patients with heart failure, and the decrease in serum T3 is proportional to the severity of the condition as assessed by New York Heart Association classification.[6] With negligible deiodinase activity, the cardiac myocytes are particularly vulnerable and depend on plasma T3.[7] Low free T3 levels have been associated with larger heart chambers and worse left ventricular systolic function. Hypothyroidism can also lead to malfunction of cardiac rhythm management devices by increasing pacing thresholds, resulting in loss of capture that can be corrected by hormonal repletion.[9,10] Among patients receiving cardiac resynchronization therapy (CRT), those with hypothyroidism had significantly higher all-cause mortality and heart failure hospitalizations compared to patients with euthyroid status, thus blunting the impact of this otherwise proven intervention.[11] Interestingly, the beneficial effect of CRT on thyroid function was documented in a small study in which CRT recipients had improvements in free T3 levels and free T3/free T4 ratio, regardless of reverse cardiac remodeling.[12]

With negligible cardiac myocyte deiodinase activity as well as impaired peripheral conversion of T4 to T3, it appears reasonable to treat with T3 instead of T4 in the setting of congestive heart failure and post-ischemic myocardium. Currently, direct assessment of tissue TH level is not possible and is extrapolated from plasma hormone levels. Thyroid stimulating hormone (TSH) may not be the best laboratory test in this setting since, in many nonthyroidal conditions, free T3 levels have been found to be low with normal TSH and free T4 levels—a fact that may hold significance in cardiovascular ailments. A biomarker reflecting intracardiac TH signaling or functional status may help formulate a therapeutic approach. It is also noteworthy that preclinical studies have documented T3 to be well tolerated without any significant arrhythmias, myocardial ischemia, or hemodynamic instability.[13] An animal model of chronic cardiac unloading demonstrated that treatment with physiological doses of T3 restored the expression of $Ca^{++}$ cycling and handling proteins and contractile function of cardiac myocytes.[14]

Treatment with TH may be a potential strategy to protect post-ischemic damaged myocardium from pathological growth and remodeling, with beneficial changes in myocyte shape, microcirculation, and collagen. An ongoing study—ThiRST (Thyroid Hormone Replacement therapy in ST elevation myocardial infarction-European Community ITC-STREP FP7 PONTE Research Project)—aims to investigate the safety and feasibility of TH replacement in patients with ST elevation myocardial infarction and to determine effects on post-ischemic remodeling, left ventricular function, and clinical outcomes (cardiac and noncardiac death, coronary revascularization, hospitalization).

At this point, more studies are needed to explore the full therapeutic potential of thyroid hormones, specifically T3, for treatment of cardiac myocyte injury in a post-ischemic state and heart failure. In addition, thyroid function may have a role in the optimal functioning of devices such as pacemakers and CRT. It is indeed intriguing to hypothesize that a low T3 state in cardiac tissue, with its regulation of many structural and functional genes, is part of a vicious pathophysiological pathway that sustains cardiac remodeling and leads to an increase in mortality.

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