CONCISE REVIEW

Alterations in thyroid hormones that accompany cardiovascular disease

Some of the most characteristic signs and symptoms of thyroid disease are those resulting from the effects of thyroid hormone on the heart and cardiovascular system. Many published reports have noted that the clinical findings resulting from excess thyroid hormone are more pronounced and prevalent than those resulting from thyroid hormone deficiency. Thus palpitations and tachycardia are reported in the majority of patients with hyperthyroidism whereas in hypothyroidism, the decrease in exercise tolerance, rise in diastolic blood pressure and decreases in cardiac contractility are much more subtle findings.

Thyroid hormone affects almost every tissue and organ system in the body, regulating basal metabolism and tissue thermogenesis (1; 2). Hyperthyroidism, either exogenous (resulting from over treatment) or endogenous (usually Graves' disease) causes predictable changes in cardiovascular hemodynamics (3). Excess thyroid hormone leads to predictable decreases in systemic vascular resistance (SVR) and increases in resting heart rate, left ventricular ejection fraction, cardiac contractility and mass, blood volume and cardiac output. The increased systolic, and decreased diastolic, blood pressure causes a widened pulse pressure. The symptoms of exercise intolerance and dyspnea are due to an inability to further increase heart rate or ejection fraction or further lower SVR in response to increased muscular work. In addition, respiratory and skeletal muscle weakness as well as a rise in pulmonary artery pressure can impair maximum exercise capacity. The reduction in SVR is mediated by a direct effect on vascular smooth muscle in peripheral arterioles which decreases mean arterial pressure. Blood volume is increased through activation of the renin-angiotensin-aldosterone system and increased renal sodium absorption. Triiodothyronine (T_3) also increases erythropoietin synthesis, which leads to an increase in red cell mass. Together, these changes increase blood volume and preload. Cardiac output may increase by 50% to 300%. The rate of left ventricular (LV) relaxation (as measured by isovolumic relaxation time), and LV filling are enhanced by the effects of thyroid hormone. LV hypertrophy results from sustained volume overload and the resulting increase in cardiac work load.

The effects of hypothyroidism are diametrically opposite to those of hyperthyroidism. Patients with the former have decreased cardiac output, bradycardia, narrowed pulse pressure and mild hypertension with increased SVR with decreased ventricular filling and diastolic relaxation. Symptoms are not specific and include fatigue, weight gain and cold intolerance, all of which are reversible with thyroid hormone replacement. Hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins (LDL) and apolipoprotein B due to alterations in lipid metabolism. Therefore, hypothyroid patients have increased risk of cardiovascular disease and an apparent increase in risk of stroke as well.

The cellular mechanisms of thyroid hormone action are mediated by nuclear thyroid hormone receptor proteins which regulate the transcription of many important genes. Thyroid hormone receptors belong to the superfamily of steroid receptors but are unique in that they are bound to response elements in the promoter regions of target genes in the absence as well as presence of T_3, unlike steroid receptors which are anchored in the cytoplasm until they bind their specific ligands. The transport of thyroid hormone into cells has been the topic of much recent investigation. Unlike many cell types including the liver, pituitary and skeletal muscle, it appears that the cardiac myocyte transports T_3 in marked preference to T_4 (4). In recent studies from our laboratory, T_3 and not T_4 is transcriptionally active in regulating the expression of important myocyte genes (5). Thus in the presence of normal serum T_4, but low serum T_3, there are alterations in cardiac gene expression which are similar to that of primary hypothyroidism as well as chronic congestive heart failure (HF). In the heart, T_3 target genes include those whose expression is also altered in heart failure as will be discussed below.

The thyroid gland produces primarily thyroxine (T_4) and to a lesser degree, T_3. The majority of serum T_3 is derived from 5'-monodeiodination either in the kidney and liver (D1) or from skeletal muscle (D2). A variety of factors including proinflammatory cytokines have been identified which impair the ability of the deiodinase enzyme system to metabolize T_4 which leads to decreased serum T_3 content (6). Previously this group of conditions was referred to as the sick euthyroid syndrome however, in light of recent evidence, the term low T_3 syndrome or nonthyroidal illness appears to be more appropriate. This conclusion derives from the fact that in many of these acute and chronic illnesses low T_3 levels may result in physiologic impairment questioning the appropriateness of the term "euthyroid."

Dating back to the first observations by Hamilton and colleagues (7), it has been shown that altered T_4 metabolism occurs in patients with HF. In almost all cases, the low serum T_3 levels are accompanied by normal thyroid stimulating hormone (TSH) and T_4. In Table 1 we have reviewed the variety of cardiac disease states that have been reported to alter thyroid hormone metabolism. This list has recently been expanded to include the unique group of patients with stress cardiomyopathy as reported by Lee et al. (8) and reviewed in this issue of Clinical Thyroidology. While their careful description of these changes in thyroid hormone metabolism are of interest, it begs the question as has been raised with other cardiac disease states, of whether thyroid hormone replacement, specifically T_3, can be a useful and novel treatment modality to facilitate improvement and recovery of cardiac function in these patients.

Table 1. Cardiovascular disease states that alter thyroid hormone metabolism

- Acute myocardial infarction
- Acute viral myocarditis
- Stress cardiomyopathy
- Heart failure – in proportion to the degree of severity
- Coronary artery bypass surgery
- Congenital heart disease surgery
- Amiodarone treatment (not dronedarone)

Table 2. Similarities between hypothyroidism and heart failure

Characteristics	Hypothyroidism	HF
Cardiac output	↓	↓
Cardiac contractility	↓	↓
Serum T_3 levels	↓	↓
Ischemic heart disease	±	+++
Systemic vascular resistance	↑	↑
Response to thyroid hormone	+++	?

Table 3. Potential benefits of T_3 treatment in heart failure

- Restore serum T_3 to normal
- Improve skeletal muscle function
- Positive lusitropic agent
- Antiarrhythmic effect on QT interval
- Decrease systemic vascular resistance
- Promote reverse remodeling
- Oxygen cost of T_3-mediated increases in cardiac work less than standard cardiac active agents

To date, the evidence that T_3 treatment can be of benefit in nonthyroidal illness in the setting of cardiac disease has arisen in a number of studies. These include the early reports that iv T_3 infusion can improve cardiac output in patients with New York Heart Association Class III-IV HF and in patients with low ejection fraction after undergoing coronary artery bypass grafting. Children undergoing surgery to repair congenital cardiac defects also benefit from the restoration of low serum T_3 levels to normal via infusion of iv T_3 in the 24-72 hours postoperative period.

Thyroid hormone metabolism is altered in patients with HF or following acute myocardial infarction resulting in the low T_3 syndrome (Table 1) (9-11). In addition to potential alterations in D1 and D2, the type 3 deiodinase converts T_4 and T_3 to the inactive compounds reverse T_3 (rT_3) and diiodothyronine (T_2) respectively and a recent study reported that cardiac D3 activity was induced in the infarcted and pathologically hypertrophic myocardium in experimental animals (12-14). In patients with HF, the decrease in serum T_3 concentration is proportional to the severity of the heart disease as assessed by the New York Heart Association (NYHA) functional classification and has been shown to be the most powerful predictor of all cause and cardiac mortality in patients with cardiac disease (7; 11; 15; 16). Cardiopulmonary bypass surgery causes an induction of proinflammatory cytokines such as interleukin-6, and an acute reduction in serum T_3 levels in children and adults (10; 17; 18). Often misunderstood, T_3 administration does not impair cardiac metabolic efficiency because the increase in cardiac output is offset by the decrease in SVR and afterload. The net effect is to enhance cardiac performance without an untoward increase in oxygen demand. T_3 improves the ratio of cardiac work to myocardial oxygen consumption, a reliable measure of myocardial efficiency (19).

T_3 regulates cardiac function as well as SVR through a combination of genomic and nongenomic mechanisms. T_3 controls cardiac contractility and relaxation via multiple mechanisms including the regulation of genes in the cardiac myocyte, specifically those genes encoding the contractile proteins, α- and β-myosin heavy chain (MHC), the sodium calcium exchanger (NCX1) and the sarcoplasmic reticulum calcium activated ATPase (SERCA2). In the failing human heart, α-MHC and SERCA2 are decreased while β-MHC expression is increased (20-22). These genes are positively and negatively regulated by thyroid hormone respectively (3). The SERCA2 pump actively transports and sequesters calcium in the sarcoplasmic reticulum during diastole. Active myocardial relaxation is a function of diastolic intracellular calcium levels and the detachment of myosin heads from actin filaments which enables the sarcomeres to lengthen. Thyroid hormone induces the expression of SERCA2 and the fast myosin heavy chain isoform. Together the enhanced expression of these proteins is largely responsible for enhanced contractile function and diastolic relaxation mediated by thyroid hormone (23). In fact, the list of important cardiac genes that are altered in HF is strikingly similar to the list of genes that are altered in hypothyroidism (Table 2). Since the hypothyroid myocardium responds in a predictable manner to thyroid hormone replacement (24-26) the recent studies in both animals and man to establish a safe and effective role for T_3 replacement in a physiologic manner seems well justified. Interestingly, death from heart disease and HF usually occurs as a result of cardiac arrhythmia and in fact, the most common electrocardiographic changes associated with hypothyroidism are sinus bradycardia and a prolonged QT interval. The latter in turn predisposes to increased ventricular irritability and ventricular tachycardia. Together, this suggests that low T_3 syndrome may also contribute to the risk of death from cardiac arrhythmias in patients with heart disease and low serum T_3 levels and supports the hypothesis that T_3 treatment of heart failure with the low T_3 syndrome can provide additional beneficial effects (Table 3).

Amiodarone is a benzofuran derived Class III anti-arrhythmic that contains 30% iodine by weight. It is frequently used for the treatment of atrial fibrillation, despite the fact that it is only approved for the treatment of ventricular tachyarrhythmias. Soon after introduction it was observed that amiodarone produced predictable changes in thyroid hormone levels including decreases in serum T_3, mild and overt primary hypothyroidism and occasionally thyrotoxicosis. While it has been presumed that these effects were the result of the excess iodine load, only the recent studies with dronedarone, the iodine free congener which produces little if any alterations in thyroid function have confirmed this suspicion.

In Summary, thyroid hormone plays a critical role in the regulation of cardiac function and cardiovascular hemodynamics. The reduction in physiologic serum T_3 that occurs in HF and other cardiovascular disease states potentially further impairs cardiac function in an already compromised heart suggesting that T_3 replacement therapy may benefit patients with low T_3 syndrome.

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