The Role of Thyroid Hormone in Donation, Transplantation and Cardiovascular Disease


by

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The views of the paper do not necessarily reflect the official policy of the Forum host, the Canadian Council for Donation and Transplantation, and are not intended for publication in their current format.
Thyroid Hormone: Review of Physiology

The thyroid gland is a highly vascular ductless gland normally weighing 10–25 g. Enlargement of the thyroid gland is referred to as a goiter. A goiter may be diffuse or nodular and may be present in any state of thyroid function.

The thyroid gland is made up of thyroid follicles. Each follicle consists of many thyroid cells surrounding a central reservoir called the colloid. The colloid contains the storage form of thyroid hormones.

Two hormones are produced in the thyroid, thyroxin (T4, or tetraiodothyronine) and triiodothyronine (T3). Both T4 and T3 are largely comprised of iodine.

Thyroid hormone synthesis, storage and release are governed by thyroid stimulating hormone (TSH) from the anterior pituitary gland. In turn, TSH is regulated by thyrotropin releasing hormone (TRH) from the hypothalamus. The target tissue responses to thyroid hormone are highly variable. Both the regulation of the hypothalamic-pituitary-thyroid axis and the target organ sensitivity also depend on many other factors such as circulating cytokines and humoral mediators.

**Thyroid Hormone Synthesis**

Ingested iodine is absorbed by the small intestine and transported to the thyroid gland. Once in the thyroid gland, iodine is concentrated and incorporated into thyroglobulin (see below), to form monoiodothyronine (MIT) and diiodothyronine (DIT). MIT and DIT later combine to form either triiodothyronine (T3) or tetraiodothyronine (T4).1,2

Thyroglobulin is a protein located within the thyroid gland. It provides a peptide backbone on which the thyroid hormones may be synthesized and sequestered until needed. In the absence of thyroglobulin, the lipophilic thyroid hormones would haphazardly diffuse across the thyroid cellular membrane. T3 and T4 therefore remain in the thyroid colloid (see below) in their storage form (complexed with thyroglobulin) until the appropriate stimulus for secretion is received.1,2

The thyroid colloid is a thyroid hormone reservoir surrounded by a cluster of thyroid cells. It is here that thyroglobulin sequesters the thyroid hormones. This cluster of thyroid cells with its center of colloid is called a thyroid follicle. Thyroid follicles make up the substance of the thyroid gland (figure 1).

**Hypothalamic-Pituitary-Thyroid Regulation**

Thyroid hormone synthesis and release is regulated by the hypothalamic-pituitary-thyroid axis. The neurohormone TRH from the hypothalamus, TSH from the anterior pituitary, and T4 and T3 from the thyroid gland are the major components, forming a negative feedback loop, but many other cellular and humoral mediators are involved in this complex process.1,2
TRH is both a hormone and a neurotransmitter. It is released from the paraventricular nucleus of the hypothalamus. As a hormone, TRH primarily stimulates the release of the pituitary hormone TSH but also stimulates the release of prolactin. TRH is responsible for the circadian rhythm of TSH and hence thyroid hormone secretion. It is secreted in a pulsatile manner, which accounts for the ultradian rhythm. As a neurotransmitter, via neuronal connections with the anterior hypothalamus, TRH aids in thermoregulation, memory and hemodynamic control.

Figure 1. Thyroid colloid surrounded by follicular cells (adapted from www.thyroidmanager.org).

The release of TSH is regulated by TRH and T₄. TSH circulates in plasma unbound with a half-life of 60 minutes and is excreted by the kidneys. TSH secretion follows the circadian rhythm set by TRH, with peak values between 2:00 a.m. and 6:00 p.m. Ultradian peaks of TSH occur every 2–4 hours. In instances outside acute illness, TSH levels are the most sensitive indicator of the state of thyroid function. T₃ is responsible for the feedback inhibition of TSH at the level of the pituitary. Like TRH, TSH production and release are inhibited by elevated levels of glucocorticoids and cytokines, which may explain the variety of changes seen in acute illness.

TSH prompts the lysosomal cleavage of the thyroglobulin/thyroid hormone complex. Once cleaved, the thyroid hormones simply diffuse through the thyroid cellular membrane. They are then carried to target tissues by specific transport proteins. Thyroid binding globulin (TBG) is the most important of these transport proteins.
**Thyroid Hormone Transport and Metabolism**

Every organ system requires exposure to physiologic levels of thyroid hormones for normal functioning. Thyroid hormone effects on target tissues are highly variable and depend on many factors.

Although both T₃ and T₄ are carried by TBG, it is the unbound fraction or free fraction that is biologically active. T₄ and T₃ are liberated from the thyroid in ratios of 20:1. Although much less T₃ is released than T₄, it is up to 8 times more biologically active. This greater bioactivity is in part explained by the fact that the proportion of unbound T₃ (free T₃ or FT₃) is greater than that of free T₄. The easier dissociation of FT₃ from TBG also explains its shorter half-life (1 day versus 7 days).¹,²

Within the target tissues, T₄ is converted to T₃ by an enzyme called 5’deiodinase. There are three types of deiodinase enzymes: types I, II and III. The target tissue conversion of thyroid hormones depends on the type of deiodinase contained therein. Type I is primarily located in the liver and kidneys and mainly degrades thyroid hormones. It is also located in the thyroid gland and is responsible for what little T₃ is released. It is the Type I enzyme that is inhibited with medication used to treat hyperthyroidism. Type II is responsible for the conversion of T₄ to T₃ in the cardiac and skeletal muscle. Type III is primarily functional in utero and converts T₃ to its inactive form, reverse T₃ (rT₃). Reverse T₃ is thought to protect the developing fetus from active maternal thyroid hormone. It is thought that the Type III enzyme may become upregulated in acute illness and may play a role in the increase in rT₃ that is seen in the nonthyroidal illness syndrome (NTIS).¹–⁴

**Thyroid Hormone Receptor Binding**

Once the target tissues are reached, the resulting activity depends on the intranuclear thyroid receptor.

The thyroid receptor and subsequent genomic activity are extremely complex. The thyroid receptor is composed of both an alpha portion and a beta portion. In turn, there are two types of alpha and two types of beta portions. One type of alpha and one type of beta portion combine to form the receptor. Therefore, the receptor may come in at least 4 forms. Further diversity comes from the fact that upon binding with thyroid hormone, each receptor complexes with another receptor (each thyroid hormone binds to two thyroid hormone receptors). Receptor binding is even further complicated by the fact that an unbound thyroid hormone receptor may complex with a nonthyroid hormone receptor and in fact has inhibitory properties (unbound receptors may inhibit genomic activity). It is this vast variation in thyroid hormone receptors and numbers in the target tissues that accounts for the diversity of symptoms of thyroid disease states.¹,⁵

Upon binding, the hormone/receptor complex binds to a DNA thyroid response element with subsequent transcription of specific genes to yield target-tissue responses.¹,² Thyroid hormone effects on target tissues are varied and have been well established through the study of thyroid disease states. As the focus of this review is the use of thyroid hormone in cardiac disease states, the effects on myocardial function will be discussed in more detail.
Thyroid Hormone Effects on Myocardial Function

Thyroid Hormone Activity in the Healthy Heart

Thyroid hormone has both direct and permissive activity on myocardial function. The effects of thyroid hormone on the heart have been well illustrated by invasive and noninvasive studies in thyroid disease states. When in excess, thyroid hormones have positive inotropic and chronotropic effects on the myocardium, but cause only a mild degree of hypertension.\(^6,7\)

The increase in cardiac output seen in hyperthyroidism is a culmination of factors.

First, the increase in heart rate promotes an increase in cardiac output via a permissive effect caused by the upregulation of beta-adrenergic receptors.\(^6\) The increase in beta-adrenergic activity also promotes hypercatabolism, which causes a mild accumulation of lactate and CO\(_2\) in tissues, resulting in vasodilatation (endocrine physiology).\(^1\)

Vasodilatation is the second factor contributing to the increase in cardiac output and is also multi-factorial:

i. The excess thyroid hormone increases non-shivering thermogenesis (raises body temperature and basal metabolic rate) by inducing the expression of an uncoupling protein (UCP-3). UCP-3 is located in the inner mitochondrial membrane of skeletal myocytes. Thyroid hormone increases UCP-3 activity by upregulation of the beta-3 adrenergic receptor (usually found on brown adipose tissue). When activated, UCP-3 uncouples the electron transport chain (which is responsible for the cellular generation of adenosine triphosphate, or ATP). Once uncoupled, the proton gradient is discharged as heat instead ATP, resulting in vasodilatation.\(^1\)

ii. Thyroid hormone may have direct vasodilatory effects on vascular smooth-muscle cells.\(^8\)

Third, thyroid hormone increases blood volume by stimulating the production of erythropoietin and by causing activation of the renin-angiotensin-aldosterone axis in response to vasodilatation (see below).\(^2,6\)

Finally, T\(_3\) improves myocardial contractility by increasing production of the alpha-myosin heavy chain isomer and by increasing the sarcoplasmic reticulum calcium-ATPase (SERCA) activity, resulting in increased intracellular calcium and the generation of a faster and stronger contraction.\(^9,10\)
Thyroid Hormone Activity in the Failing Heart

The nonthyroidal illness syndrome (NTIS, or sick euthyroid syndrome) may present with a variety of laboratory findings reported as low T₃ syndrome, low T₃–low T₄ syndrome, high T₄ syndrome or other abnormalities.⁴ Low serum T₃ is by far the most common abnormality and is seen in up to 70% of hospitalized patients.⁴ A low T₃ predicts increased mortality in advanced congestive heart failure.¹¹ The low T₃–low T₄ syndrome is observed more frequently in critically ill patients and correlates with a poorer prognosis.¹² A T₄ value of < 2–4 µg/dl imparts up to an 80% increase in the probability of death.³ TSH is often normal; however, one could argue that a normal TSH in the context of abnormal FT₄ and FT₃ is clearly abnormal.

Thyroid hormone secretion and conversion are altered in critical illness, in starvation and following surgical procedures.¹,¹³ The failing heart is one of many instances where these alterations in thyroid function tests are seen.³ NTIS has long been thought to be of no clinical significance or perhaps even adaptive. The consensus has been to re-evaluate the indices in 4–6 weeks and not to provide thyroid hormone replacement of low values. More recently, however, the concept of sick euthyroid syndrome has been suggested to be a misnomer and thus potentially dangerous.³,⁴

There are a multitude of complex interactions that may account for the alterations in thyroid indices. Alterations in hormone production, secretion, transport and binding at each level of the hypothalamic-pituitary-thyroid axis have been described.³ In a study by Van den Berghe and colleagues, thyroid axis hormone levels demonstrated variability at different stages of acute illness.¹³ In the first 5–7 days there is an initial elevation followed by an abrupt decline in TSH in conjunction with low FT₄ and FT₃ levels. After seven days of critical illness, all three levels continue to fall. With recovery, TSH levels rise to above-normal levels as thyroid hormone levels normalize. The rise in TSH is followed by normalization of all three hormones.¹³ A further study by Van den berghe and colleagues has demonstrated that the hypothalamus may be at the root of the inappropriately normal TSH observed. In this study, the administration of TRH to patients with severe NTIS (low TSH, FT₄, FT₃) resulted in an increase in TSH, T₄ and T₃ levels.¹⁴ Clinical endpoints were not evaluated. Finally, other circulating hormones and cytokines have complex interactions at all levels of the axis and probably contribute to the variability of thyroid axis hormone levels.³

Several studies in the 1980s and early 1990s evaluating treatment of the NTIS in acute critical illness have failed to demonstrate any clear benefit.⁴ No recent studies in acute and chronic critical illness have been conducted. To date, the NTIS is neither routinely investigated nor routinely treated in acute care practice. In concrete terms, a low-serum T₃ with or without a low-serum T₄ is a state of hypothyroidism at the cellular level regardless of the TSH. By this logic, treatment seems worthy of consideration.
Thyroid Hormone Replacement in the Critically Ill

As discussed, in healthy adults the thyroid gland produces all circulating T₄ and 20% of circulating T₃.¹,¹⁵ The balance of T₃ is produced by peripheral conversion of T₄ to T₃ by deiodination. In times of stress—such as in critical illness, in heart failure and following cardiac surgery—the enzymes responsible for deiodination become inhibited. Circulating inflammatory mediators have been implicated in this process and in the suppression of the hypothalamic-pituitary-thyroid axis. Furthermore, the Type III deiodinase may become upregulated, which may account for the elevated levels of the inactive form of T₃ (rT₃ or reverse T₃).¹,³,⁴

Perhaps the best and only model for the use of thyroid hormone replacement therapy in critical illness is myxedema coma. This therapy for myxedema coma remains a controversial issue in thyroidology. The main controversy concerns whether to administer T₄ alone, T₃ alone or a combination of the two. Because myxedema coma is rare, there are no randomized controlled trials to guide therapy.

Because gastric blood flow and hence absorption may be impaired in times of stress, many clinicians advocate parenteral administration of thyroid hormone. Some advocate the use of T₄ because the conversion of T₄ to T₃ provides a slow and steady onset of action. However, the likelihood of impaired Type I deiodinase activity (the enzyme that converts T₄ to T₃), and upregulation of Type III deiodinase (which converts T₄ to inactive rT₃) brings the bioavailability into question.¹-⁴

For this reason, most clinicians advocate the use of parenteral T₃ with T₄. T₃ has a rapid onset of action but requires more frequent dosing intervals. For myxedema coma, T₃ is administered 10 µg as an initial intravenous bolus followed by 10 µg IV every 8–12 hours, and T₄ is administered 4 µg/kg lean body mass (200–300 µg) followed by 100 µg 24 hours later and then a maintenance dose of 50 µg IV per day until the patient can be converted to enteral T₄ as a single agent.²

One study from 1985 demonstrated an increase in cardiovascular mortality associated with high serum concentrations of T₃ when it was used alone.¹⁶

In Canada, the enteral form of T₃ and T₄ and parenteral T₄ are all readily available and inexpensive (table 4). Parenteral T₃ is not commercially available in Canada. It is available in the United States and also through Health Canada’s special access program. The hospital pharmacist may also prepare parenteral T₃ by dissolving L-T₃ in 0.1N NaOH followed by a 10-fold dilution with normal saline containing 2% albumin. The final concentration of T₃ is 25 µg per milliliter.¹⁷ It is recommended that pharmacists considering preparing parenteral T₃ undertake in-house sterility and stability testing.
Thyroid Hormone Use in Cardiac Disease States

Studies of physiology and pathophysiology have clearly demonstrated the positive effects of thyroid hormone on the myocardium. It is therefore logical to examine the possibility that thyroid hormone may have positive effects on a failing or acutely stressed heart. Several randomized controlled trials have looked at thyroid hormone replacement in adults in the context of heart failure, heart transplant and cardiopulmonary bypass and in children having congenital heart surgery.

Review of the Literature

The main focus of the literature search was to identify articles to answer two questions about the value of hormone replacement therapy in cardiac disease states pediatric and adult populations: (1) Is there evidence for thyroid hormone deficiency? (2) If there is evidence for thyroid hormone deficiency, is there any evidence to support replacement therapy?

A search was done in MEDLINE from 1966 to the second week of January 2004 and in other in-process and non-indexed citations. Articles pertaining to thyroid hormone were searched using the MeSH terms “thyroid hormone”, “T4”, “tetraiodothyronine”, “T3”, “triiodothyronine”, “L-thyroxine” and “synthroid”. To retrieve articles pertaining to cardiac surgery, the following MeSH terms were used: “cardiac surgery”, “open heart surgery”, “CPB”, “cardiopulmonary bypass”, “valvular surgery”, “bypass surgery”, “coronary artery bypass surgery” and “CABG”. These two searches were then combined and limited to randomized, double blind, placebo controlled trials reported in English-language publications.

To find articles related to thyroid hormone use in heart transplant and congestive heart failure, a combined search was done using the above MeSH terms for thyroid hormone plus the terms “heart transplant”, “cardiac transplant”, “congestive heart failure”, “CHF”, “congestive cardiac failure”, “CCF” and “heart failure”. Again, search results were limited to randomized controlled trials and English publication.

In addition to the above papers, selected articles were chosen where thyroid hormone indices, converting enzymes and receptors were measured in the appropriate contexts (congestive heart failure, cardiac surgery or heart transplant).
Summary of the Evidence

Nine trials were identified. Two of the trials were performed in children undergoing congenital heart surgery, one study was of adult congestive heart failure, and one study was of heart transplant recipients. The remainder of the trials were in adult coronary artery bypass grafting using cardiopulmonary bypass.

Question 1: Is there evidence for thyroid hormone deficiency?

In endocrinology practice, thyroid dysfunction is both a clinical and a biochemical diagnosis. The borders of absolute diagnoses have become blurred since the recognition of subclinical disease. Subclinical hypothyroidism is characterized by a slightly elevated TSH. Thyroid hormones FT$_4$ and FT$_3$ remain within the normal range. These patients often have no symptoms of hypothyroidism. In the past, treatment would not be offered; however, more recent evidence supports a link between subclinical hypothyroidism and elevated LDL cholesterol. There is also some conflicting evidence of an increased risk of myocardial infarction in untreated cases.

In patients who have chronic congestive heart failure, who are brain dead or who have just undergone cardiac surgery or transplant, the signs and symptoms of hypothyroidism are even more difficult to tease out. Biochemical markers are the only means by which to investigate. However, as previously discussed, these patients may demonstrate the so-called sick euthyroid syndrome. Perhaps, as in subclinical hypothyroidism, this diagnosis may be a misnomer.

T$_3$ deficiency is present in up to 85% of donors and is thought to be a contributing factor in donor heart dysfunction following heart transplant. Not surprisingly, T$_3$ levels are significantly lower in candidates who require inotropic support or mechanical assistance in the intensive care unit.

In one study of 14 patients with severe heart failure secondary to ischemic or dilated cardiomyopathies, a statistically significant upregulation of myocardial thyroid hormone receptor isoforms was demonstrated. In this study, myocardial biopsies just prior to orthotopic heart transplants were compared to biopsies taken from patients undergoing single-vessel coronary artery bypass with ejection fractions > 50%. This upregulation may be interpreted in two ways. First, it may imply that the failing heart compensates for a relative lack of thyroid hormone by increasing its receptor availability. Conversely, the upregulation may also indicate a protective mechanism in that by increasing the number of thyroid hormone receptors, the higher proportion of unbound receptors will inhibit transcription.

Thyroid hormone profiles in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) show a decline in total T$_4$ and T$_3$ after initiation of CPB. This decline may be attributed to hemodilution. Not surprisingly, patients demonstrate a picture of the NTIS following surgery. The cause for the NTIS is multifactorial and probably relates to the multitude of circulating cytokines and corticosteroids. The pattern slowly improves up to the 6th postoperative day. It is of interest that at least one study has demonstrated that patients with higher concentrations of T$_3$, T4 and TSH in the postoperative period suffered fewer major postoperative complications and death. Furthermore, patients who showed no increase in T$_4$ or T$_3$ after surgery had markedly increased risk of complications and death.
Biochemically, studies in bypass surgery consistently demonstrate evidence of the NTIS. However, that same biochemical profile may also suggest a transient state of hypothyroidism.

**Question 2: Is there evidence to support thyroid hormone replacement?**

**Trials of thyroid hormone use in heart transplantation.** In a two-part trial published in 1997 by Jeevanandam, intravenous T₃ replacement therapy was evaluated as adjunctive therapy for both the donors and the recipients in heart transplantation.²¹

The first part of the study was a non-blinded, placebo-controlled trial where repeated bolus doses of intravenous T₃ were given to two groups of donors. In this trial, 0.4 µg/kg of T₃ was administered every hour until time of harvest to a maximum dose of 1.2 µg/kg and compared to matched placebo. Treatment groups were markedly and intentionally different at baseline. The treatment group consisted of 22 young potential donors with significant myocardial dysfunction, 18 of whom had been rejected by other institutions. The placebo group consisted of 52 donors with adequate myocardial function (EF = 39 ± 5.5 versus EF = 58 ± 3.2, respectively; p = < 0.05). Of the original 22 hearts in the treatment group, 5 were eventually declined for transplantation. None of the hearts in the control group was declined.²¹

Postoperative day 1 to day 6, the treatment group required more inotropes and at higher doses than the control group (10/17, or 59% versus 15/52, or 28%, respectively; p = < 0.05). All patients survived to week 1 and were off inotropic support within 6 days. At day 7, cardiac index and ejection fractions were similar in both groups (2.8 ± 0.6 versus 2.9 ± 0.8 for cardiac index; 57.2 ± 4.5 versus 53.2 ± 3.2 for EF in treatment versus placebo groups, respectively; p = NS). At six months, there were two deaths in each group due to acute rejection. Amongst survivors, ejection fractions were similar in both groups (59.0 ± 2.2 versus 56.0 ± 4.5 for treatment versus placebo, respectively; p = NS).²¹

The second part of Jeevanandam’s study was a randomized, blinded, placebo-controlled trial of T₃ administration to 19 men and women between the ages of 37 and 59 who received heart transplants. In this study, a 0.4 µg/kg initial bolus dose of intravenous T₃ at the time of reperfusion (release of aortic cross clamp) was followed by a six-hour infusion of 0.8 µg/kg/hr and compared to matched placebo. Inotropic support was administered to both groups by a protocol. If the protocol failed to maintain a cardiac index of > 2.5, a non-blinded dose of T₃ was given. The transplant recipient groups were similar in terms of age, weight, inotropic requirements and cardiac indices.²¹

Patients in the treatment group required less inotropic support when compared to those in the placebo group (1/10, or 10%, versus 6/9, or 67%, respectively; p = < 0.05). Furthermore, no patients in the treatment group required the non-blinded dose of T₃ whereas 4 patients in the placebo group did (p = < 0.05). In addition, the duration of inotropic requirements was shorter in treatment versus placebo groups (2.5 ± 0.5 versus 3.4 ± 0.6, respectively; p = < 0.05). All patients survived to hospital discharge; however, patients in the treatment group had shorter lengths of stay in the ICU than did patients who received placebo (2.9 ± 0.4 versus 4.5 ± 0.6, respectively; p = < 0.05) (table 1).²¹
It should be noted that these trials were not consecutive and did not examine intravenous administration of T₃ to donors followed by continued administration to recipients. To date, no trial has examined this aspect of donor/recipient thyroid replacement therapy.

On the cellular level, one concern in heart transplantation is the exposure of the myocardium to high levels of endogenous or exogenous catecholamines or both, which may impair contractile performance. In one study, isolated trabeculae were taken from atrial myocardium from 15 patients undergoing coronary artery bypass surgery. The trabeculae were exposed to a solution of epinephrine for 6 hours followed by a solution of T₃ for 30 minutes. After 6 hours of catecholamine exposure there was an expected 56.8% (p = 0.0001) decline in isotonic force and 54% decline in isotonic shortening (p = < 0.1) when compared to controls. After 30 minutes’ exposure to T₃ there was a significant recovery of isometric force (p = < 0.1) and isotonic shortening (p = < 0.005).²⁵

**Trials of thyroid hormone use in the congestive heart failure.** One double-blind, randomized, placebo-controlled trial was found that was published following a pilot study to examine safety and dosing.²⁶ In this trial, an intravenous T₃ analogue, 3,5-diiodothyronpropionic acid (DITPA), was compared to placebo in 19 patients (mean age 62) with moderately severe heart failure (NYHA class II and III heart failure). Groups were similar at baseline except for a significantly lower ejection fraction in the treatment group compared to the placebo the group (18.1 ± 2.4 versus 28.7 ± 1.9, respectively; p = 0.003). Patients were randomly assigned to receive either 1.875 mg/kg DITPA or placebo daily for 2 weeks followed by an increase to 3.75 mg/kg daily for an additional 2 weeks.²⁶

Patients in the treatment group demonstrated an average increase in cardiac index of 17% and a decrease in systemic vascular resistance (percentage not provided) after the four-week trial compared to no significant change in the placebo group (p = 0.04 and p = 0.02, respectively). There were no side effects or adverse events reported (table 1). These findings may imply that DITPA has the most benefit in patients with low cardiac parameters; however, the numbers are too small to be certain. DITPA has yet to undergo phase III trials and remains unavailable in North America.

One clinical trial in which no randomization or blinding was performed and no placebo control group was used merits consideration. This trial, published in 1998, by Hamilton and colleagues, examined the effects of various doses of intravenous T₃ in patients with severe heart failure (NYHA class III and IV).²⁷ Twenty-three patients assigned to 7 different groups (n = 1–6 patients per group) received various doses and durations of intravenous T₃ ranging from 0.01–0.7 μg/kg initial bolus ± an infusion for up to 12 hours. The numbers in each group are far too small to evaluate statistical significance; however, of note, patients who received the largest dose for the longest duration had a significant increase in cardiac output (3.0 ± 0.6 to 4.0 ± 1.0 L/min ; p = 0.003) with a reduction in systemic vascular resistance (2.291 ± 1.022 to 1.664 ± 629 dynes/sec/cm⁵; p = 0.02).²⁷

**Trials of thyroid hormone use in adult cardiopulmonary bypass.** Five double-blind, randomized, placebo-controlled trials were found that compared the use of intravenous T₃ to placebo (table 2). Doses ranged were from 0.4 μg/kg bolus to 0.8 μg/kg bolus. Infusion rates were continued for 6 hours in 4 trials and doses ranged from 0.1 μg/kg/hr to 0.12 μg/kg/hr.²⁸–³¹ One study used repeated bolus doses ranging from 0.05 to 0.2 μg/kg at various times during and
within the first 24 hours following surgery. All trials were performed in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass and ranged in size from 20 to 211 patients. Three trials looked at high-risk patient populations with ejection fractions < 30–40%. None of the trials demonstrated any statistically significant changes in length of stay or death. There were no harms or adverse effects reported in association with the use of T₃; specifically, there was no increase in the risk of atrial fibrillation. The measurements that reached statistical significance in more than one trial were cardiac index and systemic vascular resistance.

Three trials showed a statistically significant improvement in cardiac indices in patients who received intravenous T₃. The first trial, by Mullis-Jansson and colleagues, included 170 patients (81 randomized to receive intravenous T₃; 89 assigned to placebo) with mean ejection fractions of 39% who underwent elective coronary artery bypass surgery. The initial bolus dose of T₃ administered just after the release of the cross clamp was 0.4 µg/kg followed by an infusion at 0.1 µg/kg/hr. Subjects who received T₃ consistently showed a significantly higher cardiac index and lower inotropic requirements for up to 12 hours following surgery when compared to placebo (3.01 ± 0.58 versus 2.80 ± 0.64 for cardiac index, respectively; p = 0.001). When compared to the placebo group, these patients also had a lower incidence of postoperative myocardial infarction (4% versus 18%; p = 0.007), pacemaker dependence (14% versus 25%; p = 0.013) and need for mechanical support with intraaortic balloon pump or left ventricular assist device (7 patients versus 0 patients; p = 0.01). There were 2 deaths in the placebo group versus no deaths in the treatment group (28).

A second trial looked at 142 patients (71 patients randomized to each group) with ejection fractions < 40% who underwent coronary artery bypass surgery. Results demonstrated an improvement in cardiac index (2.97 ± 0.72 versus 2.67 ± 0.61 L/min/m²; p = 0.007) and a decrease in systemic vascular resistance (1073 ± 314 versus 1235 ± 387 dynes/sec/cm⁵; p = 0.003) when a bolus dose of T₃ was given with the removal of the cross clamp followed by a 6-hour infusion rate at 0.113 µg/kg/hr. In addition, when compared to the placebo group, these patients had a lower incidence of atrial fibrillation (24% versus 46%; p = 0.009). Novitsky and associates performed two small trials comparing T₃ in patients with ejection fractions < 30% to T₃ in patients with ejection fractions > 40%. Dosing of intravenous T₃ for these two studies was highly variable. In the study of patients with lower ejection fractions, 24 men and women were randomized to receive either a matched placebo or an initial bolus dose of 0.1 µg/kg during cardiopulmonary bypass followed by a second bolus dose of 0.075 µg/kg 5 minutes following CPB. Two further doses of 0.05 µg/kg were given at 4 and 8 hours following surgery. At the end of the trial they were unable to detect any significant differences in hemodynamic parameters; however, the patients in the treatment group required less inotropic support up to 24 hours following surgery (p = < 0.01).

For patients with ejection fractions > 40%, (n = 13 in treatment group; n = 11 in control group) the dosing regimen was as follows: initial bolus of 0.2 µg/kg during CPB followed by 0.15 µg/kg bolus at 4 hours following surgery; 0.1 µg/kg at 8 hours postoperatively; and 2 further doses of 0.05 µg/kg at 12 and 20 hours following surgery. At the end of the study the researchers documented a statistically significant improvement in the cardiac output (L/min) in the treatment
group over those randomized to receive placebo, which was evident up to 24 hours postoperatively (CI ~5.5L/min versus 4.0L/ min, respectively; \( p = < 0.02 \) at 24 hours). \(^{32}\)

Two trials showed a decrease in systemic vascular resistance that reached statistical significance in patients who received T\(_3\). \(^{29,30}\) The first trial, by Klemperer, was reviewed above. In the second study, 60 patients with ejection fractions < 40% undergoing elective coronary revascularization were randomized to receive an intravenous bolus of T\(_3\) of 0.8 \(\mu\)g/kg followed by an infusion of 0.113 \(\mu\)g/kg/hr for 6 hours (\( n = 30 \)) versus matched placebo (\( n = 30 \)). The researchers found a statistically significant decrease in the systemic vascular resistance in patients who received T\(_3\) when compared to placebo (1040 ± 220 versus 1350 ± 420, respectively; \( p = < 0.001 \)). Although there was not a statistically significant improvement in the cardiac index, there was a notable trend in the treatment group (2.75 ± 0.52 versus 2.63 ± 0.6, respectively; \( p = \text{NS} \)). \(^{30}\)

One trial where 137 patients were randomized to receive 0.8 \(\mu\)g/kg of an initial bolus dose of T\(_3\) at the release of the aortic cross clamp followed by an intravenous infusion of 0.12 \(\mu\)g/kg/hr for 6 hours or matched placebo failed to show any statistically significant changes in cardiac indices or any need for inotropic drug support. \(^{31}\)

**Trials of thyroid hormone use in pediatric congenital heart surgery.** In a randomized, double-blind, placebo-controlled study by Bettendorf and associates (2000), \(^{33}\) 40 children and young adults between the ages of 2 days and 10.4 years who were scheduled to undergo cardiac surgery for congenital heart defects were randomized to receive either intravenous T\(_3\) or placebo for up to 12 days.

For their primary outcome of echocardiographic variables of left ventricular function, the children randomized to IV T\(_3\) who had longer surgical procedures with prolonged cardiopulmonary bypass demonstrated a significant increase in the mean change in their cardiac index when compared to children randomized to placebo (20.4% [SD 19.6] versus 10.0% [SD 15.2]; \( p = 0.004 \)). This increase in cardiac index was even more remarkable in the children who had a longer surgical procedure with prolonged cardiopulmonary bypass (table 2). There were also non-statistically significant trends towards shorter lengths of stay in the intensive care unit, smaller postoperative catecholamine doses and shorter periods of mechanical ventilation. There was no reported increase in adverse events. \(^{33}\) This study was limited by the small number of participants and the wide variety of procedures, with the 40 children undergoing at least eight different types of surgical interventions of varying complexity and duration. \(^{33}\)

In a second trial also published in 2000, Portman and colleagues studied the effects of intravenous T\(_3\) on 14 infants less than 1 year of age who were scheduled to undergo surgical repair of either a ventricular septal defect or tetralogy of Fallot. \(^{34}\) The children randomized to treatment received a 0.4 \(\mu\)g/kg dose of T\(_3\) immediately before the start of cardiopulmonary bypass and then a repeated dose at the onset of reperfusion. The treatment group was found to have improved myocardial oxygen consumption as indicated by an elevation in heart rate and hence systolic pressure rate product after 6 hours. There was no difference in inotropic drug requirements. One patient was reported to have a brief episode of supraventricular tachycardia in the treatment group. \(^{34}\)
Perspective

Thyroid hormone has well-established physiologic effects on myocardial function during homeostasis. As with most hormone systems, the balance of the hypothalamic-pituitary-thyroid axis alters in times of stress.

Thyroid hormone exerts its effects in two ways. The first way is a direct effect, which may be seen immediately. The second requires genomic alterations, which may take hours to days. As discussed, thyroid hormone receptor binding is extremely complex and highly variable. In addition, the hypothalamic-pituitary-thyroid axis is much more complex than simply a feedback loop between three hormones and three locales. As with all endocrine systems, the hypothalamic-pituitary-thyroid axis interacts with all other endocrine systems and is in a constant state of flux. Furthermore, the actions of thyroid hormones go beyond serum hormone levels and receptor binding as they also depend on carrier proteins and enzymatic conversion. These factors make thyroid hormone action difficult to predict even in homeostasis.

In acute stress, the alterations in inflammatory mediators and in virtually every hormone make this already complicated system even more complex. For this reason it is not surprising to see inconsistent results from studies of small populations using variable doses and dosing intervals. To assume that one dose will work for all patients in times of stress is to assume that all patients have similarities in receptor binding, postreceptor signalling and enzymatic conversion and similar levels of all other inflammatory mediators and hormones.

It is impossible to imagine that a hormone this complex is simply another inotrope, as only one of its many actions is to upregulate beta-adrenergic receptors. Because of its complex interactions, it is also difficult to imagine that thyroid hormone will be the one and only hormone that improves morbidity and mortality.

As the endocrine systems are being studied with more scrutiny in the context of acute illness, notable deficiencies are evolving into syndromes such as relative adrenal insufficiency, vasopressin deficiency and hyperglycemia/insulin resistance. As the treatments of these newly discovered syndromes have proven benefits in reducing mortality, perhaps it is time to revisit the treatment of the NTIS. 35–37

As for the potential to do harm, any hormone excess or deficiency has this potential, but providing thyroid hormone replacement may be the best way to do no harm. Nonetheless, one must remain mindful of the potential harm in providing too much exogenous thyroid hormone to patients with compromised cardiac status. Either way, although they may not have any proven benefit as yet, physiologic doses of T3 in patients with cardiac failure or following cardiac surgery are unlikely to cause harm.

That being said, it is of interest that the populations who seemed to benefit most in the studies reviewed were the high-risk coronary artery bypass patients, children with prolonged surgery and cardiopulmonary bypass and patients with advanced congestive cardiac failure. Perhaps these findings point towards populations to study in more detail with a larger trial.
## Tables

### Table 1. Summary of trials of DITPA use in congestive heart failure and intravenous T₃ in heart transplant recipients

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Procedure</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Treatment vs Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morkin₂⁶</td>
<td>19</td>
<td>Congestive Heart Failure</td>
<td>1.875mg/kg DITPA X 2 weeks</td>
<td>Atrial fibrillation</td>
<td>No difference</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.75mg/kg DITPA X 2 weeks</td>
<td>Cardiac index</td>
<td>Improved</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Decreased</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>No difference</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>No difference</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>Not assessed</td>
<td>NA</td>
</tr>
<tr>
<td>Jeevanandam₂¹</td>
<td>74</td>
<td>Heart Transplant Donors (poor pre-operative function)</td>
<td>0.4 µg/kg bolus each hour for a maximum dose: 1.2 µg/kg</td>
<td>Atrial fibrillation</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>Improved on T3</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>Not applicable</td>
<td>N/A</td>
</tr>
<tr>
<td>Jeevanandam₂¹</td>
<td>74</td>
<td>Heart Transplant Donors (good pre-operative function)</td>
<td>No T₃ given</td>
<td>Atrial fibrillation</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>Not reported</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>Improved on T3</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>Not applicable</td>
<td>N/A</td>
</tr>
<tr>
<td>Jeevanandam₂¹</td>
<td>74</td>
<td>Heart Transplant Recipients (6 months following transplant)</td>
<td>No T₃ given</td>
<td>Atrial fibrillation</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>No difference</td>
<td>N/R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>No applicable</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>No difference</td>
<td>N/R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>No applicable</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EF (%)</td>
<td>No difference</td>
<td>N/R</td>
</tr>
<tr>
<td>Jeevanandam</td>
<td>19</td>
<td>Heart Transplant Recipients</td>
<td>0.4 µg/kg before donor heart reperfusion</td>
<td>Atrial fibrillation</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8 µg/kg/hr X 6 hours</td>
<td>Cardiac index</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Less required</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Intervention is intravenous triiodothyronine (T₃) unless otherwise indicated; NS=not statistically significant; NR = not reported; N/A = not assessed
Table 2. Summary of trials of intravenous T₃ use in coronary artery bypass

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Procedure</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Treatment vs Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mullis-Jansson</td>
<td>170</td>
<td>Elective CABG</td>
<td>0.4 µg/kg bolus and 0.1 µg/kg infusion (6 hours)</td>
<td>Atrial Fibrillation</td>
<td>No difference</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac Index</td>
<td>Improved</td>
<td>\textbf{0.0001}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>No difference</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>No difference</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>No difference</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td>Klemperer⁵⁹</td>
<td>142</td>
<td>Elective CABG EF  &lt; 40%</td>
<td>0.8 µg/kg bolus and 0.113 µg/kg infusion (6 hours)</td>
<td>Atrial fibrillation</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>Improved</td>
<td>\textbf{0.007}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Decreased</td>
<td>\textbf{0.003}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>Elective CABG EF  &lt; 40%</td>
<td>0.8 µg/kg bolus and 0.113 µg/kg infusion (6 hours)</td>
<td>Atrial fibrillation</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>No difference</td>
<td>\textbf{&lt; 0.001}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>Decreased</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>Not assessed</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td>Bennet-Guerrero</td>
<td>211</td>
<td>Elective CABG</td>
<td>0.8 µg/kg and 0.12 µg/kg/hr for 6 hours</td>
<td>Atrial fibrillation</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>No difference</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>No difference</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>No difference</td>
<td>NR</td>
</tr>
<tr>
<td>Novitzky</td>
<td>24</td>
<td>Elective CABG (EF &lt; 30%)</td>
<td>At CPB: 0.1 µg/kg bolus</td>
<td>Atrial fibrillation</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At cross clamp removal:</td>
<td>No difference</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+5 mins: 0.075 µg/kg bolus</td>
<td>No difference</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+4 hours 0.05 µg/kg bolus</td>
<td>Less required</td>
<td>\textbf{&lt; 0.01}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+8 hours 0.05 µg/kg bolus</td>
<td>NS</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atrial fibrillation</td>
<td>No difference</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac index</td>
<td>Improved</td>
<td>\textbf{&lt; 0.009}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SVR</td>
<td>No difference</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inotropic support</td>
<td>None</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of stay</td>
<td>Not assessed</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: EF = Ejection Fraction; CABG = Coronary Artery Bypass Graft; CPB = Cardiopulmonary Bypass; SVR = Systemic Vascular Resistance; NS = Not Significant; NR = Not Reported; N/A = Not Assessed; \textbf{Bold} indicates significant results.
+12 hours 0.05 µg/kg bolus
+20 hours 0.05 µg/kg bolus

Intervention is intravenous triiodothyronine (T₃) unless otherwise indicated; NS=not statistically significant; NR = not reported

Table 3. Summary of trials intravenous T₃ use in pediatric cardiac surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Age</th>
<th>Procedure</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Treatment vs Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portman³³</td>
<td>14</td>
<td>&lt; 1 day</td>
<td>VSD repair Or Tetralogy</td>
<td>0.4 µg/kg iv bolus pre CPB and 0.4 µg/kg iv bolus post CPB</td>
<td>Atrial fibrillation Cardiac index SVR Inotropic support Death Length of stay</td>
<td>1 reported case Not assessed Not assessed No difference Not assessed</td>
<td>NS N/A N/A NS N/A</td>
</tr>
<tr>
<td>Bettendorf³⁴</td>
<td>40</td>
<td>2 days to 10 yrs</td>
<td>Varied all requiring CPB</td>
<td>2 µg/kg iv bolus POD and 1 µg/kg iv bolus daily POD1-POD12</td>
<td>Atrial fibrillation <strong>Cardiac index</strong> SVR Inotropic support Death Length of stay</td>
<td>Not assessed <strong>Improved</strong> Not assessed less none shorter</td>
<td>N/A <strong>0.004</strong> N/A NS N/A NS</td>
</tr>
</tbody>
</table>

N/A = not assessed
Intervention is intravenous triiodothyronine (T₃) unless otherwise indicated; NS=not statistically significant; NR = not reported; N/A = not assessed
Table 4. Thyroid hormone preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name (Manufacturer)</th>
<th>Route</th>
<th>How Supplied</th>
<th>Cost/day ($CAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetraiodothyronine (levothyroxine, T4)</td>
<td>Synthroid (Abbott)</td>
<td>PO</td>
<td>25, 50, 75, 88, 100, 112, 125, 150, 175, 200, 300 mcg tabs</td>
<td>0.06a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>500 mcg/10mL vial</td>
<td>30.76b</td>
</tr>
<tr>
<td></td>
<td>Eltroxin (GlaxoSmithKline)</td>
<td>PO</td>
<td>50, 100, 150, 200, 300 mcg tabs</td>
<td>0.03c</td>
</tr>
<tr>
<td></td>
<td>Cytomel (Theramed)</td>
<td>PO</td>
<td>5 and 25 mcg tabs</td>
<td>0.23c</td>
</tr>
<tr>
<td>Triiodothyronine (liothyronine, T3)</td>
<td>Triostat (King)</td>
<td>IV</td>
<td>10 mcg/ml vial</td>
<td>1966.44 (based on q8h-q6h dosing of a 10 ug dose) to 2621.91e</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>25 µg/ml</td>
<td>~1.00</td>
</tr>
</tbody>
</table>

a based on average maintenance dose of 150 mcg/day
b based on average maintenance dose of 100 mcg/day
c based on average dose of 50 mcg/day
d Triostat is not commercially available in Canada and thus is only available from the United States through the Special Access Program of Health Canada (1-613-941-2108)
e based on average dose of 10 mcg IV q6h and a conversion rate of 0.7392 $USD/$CAD
Acronyms and Definitions

FT₃  free T₃
FT₄  Free T₄
NTIS  nonthyroidal illness syndrome (sick euthyroid syndrome)
T₃  triiodothyronine
T₄  tetraiodothyronine
TBG  thyroid binding globulin
Tg  thyroglobulin
TRH  thyroid releasing hormone
TSH  thyroid stimulating hormone

Circadian rhythm: Variations seen in endocrine secretion patterns within a 24-hour period. Variations include diurnal and ultradian patterns (see below)

Diurnal variation: A pattern in endocrine secretion demonstrating two peak levels depending on the time of day.

Free T₃ (FT₃): The portion of T₃ that is unbound to carrier proteins and thus is bioavailable.

Free T₄ (FT₄): The portion of T₄ that is unbound to carrier proteins and thus is bioavailable.

Nonthyroidal illness syndrome (NTIS; sick euthyroid syndrome): A highly variable pattern of abnormalities in thyroid hormone tests seen in patients who are ill for reasons other than hyperthyroidism or hypothyroidism.

Thyroid binding globulin: The main carrier protein for T₄ and T₃.

Ultradian rhythm: A rhythmic repetitive pattern of endocrine secretion that occurs throughout the day and night.
References


