The use of thyroid hormone in cardiac surgery

Cornelius Dyke, MD

Cardiopulmonary bypass has been demonstrated to produce a state of functional hypothyroidism characterized by low levels of circulating tri-iodothyronine and elevated levels of reverse Tri-iodothyronine. This low tri-iodothyronine state may have significant hemodynamic consequences similar to that seen with chronic hypothyroidism. In a number of experimental models, evidence has accumulated suggesting that tri-iodothyronine supplementation to the ischemically injured heart enhances ventricular contractile performance. Clinically, tri-iodothyronine supplementation after cardiac surgery improves hemodynamics, although the population of patients who might benefit from this unconventional therapy remains unclear. In this article, the rationale and experimental evidence for the use of tri-iodothyronine during cardiac surgery are reviewed.

University of Pittsburgh Medical Center, Suite C 700 PUH, 200 Lothrop Street, Pittsburgh, PA 15213, USA.

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Abbreviation

T_3 tri-iodothyronine

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Interactions between thyroid hormone and the heart have been recognized for over 150 years [1]. Thyroid hormones have a profound effect on cardiac function, the peripheral vasculature, and the sympathetic nervous system, and chronic disorders of thyroid metabolism can lead to profound hemodynamic disturbances [2,3]. More recently, it has become recognized that acute changes in thyroid hormone metabolism also impact cardiovascular function. Events such as myocardial infarction, cardiopulmonary bypass, and congestive heart failure have all been demonstrated to alter thyroid hormone metabolism and have led to the use of an old drug in new ways. In this article, the experimental and clinical evidence leading to the use of thyroid hormone as a pharmacologic agent in cardiac surgery is discussed and the potential mechanisms for its use are reviewed.

Normal thyroid metabolism

An understanding of normal thyroid hormone metabolism is essential for the understanding of the rationale for thyroid hormone supplementation in cardiac surgery. Thyroid hormone synthesis occurs within the thyroid gland, where tyrosine, bound to thyroglobulin, is iodinated, yielding monoiodotyrosine and di-iodotyrosine. Coupling of these two molecules produces tri-iodothyronine (T_3), but only in relatively small amounts (less than 20% of total T_3 production occurs in the thyroid gland). Thyronine is nearly completely produced within the thyroid gland from the coupling of two molecules of di-iodotyrosine, and its production is exquisitely controlled by thyroid-stimulating hormone through a negative feedback loop (Fig. 1). The vast majority of T_3 is produced by conversion of thyronine to T_3 in the periphery, mainly in the liver and kidney. Two peripheral enzymes deiodinate thyronine: 5'-monodeiodinase converts thyronine to T_3 (3,5,3'-T_3), the active hormone, whereas 5-monodeiodinase converts thyronine to reverse T_3 (3,3',5'-T_3), a biologically inactive metabolite. Both thyronine and T_3 are tightly bound to plasma proteins. Circulating T_3 is primarily bound by thyroxine-binding globulin and (to a lesser extent) albumin. Unlike thyronine, little T_3 is bound to prealbumin. Only free, unbound T_3 (approximately 0.2% of the total T_3) is metabolically active. Tri-iodothyronine has 10 times the biologic activity of thyronine, which in effect acts as a prohormone. Reverse T_3 (3,3',5'-T_3) is biologically inert.

Various forms of thyroid hormone replacement are available in the United States. Nearly all are oral tablets for the correction of chronic hypothyroidism. Tri-iodothyronine is available in intravenous form for rapid hormone

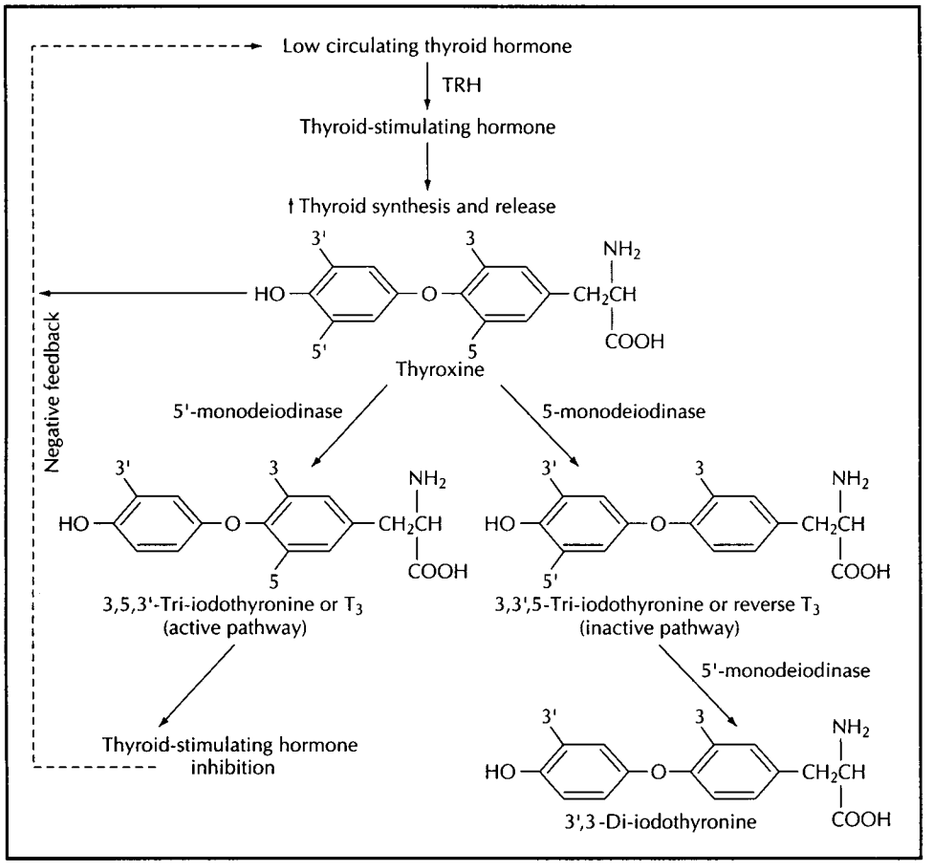

Fig. 1. Thryroid hormone synthesis and regulation. Thyroxine is produced in the thyroid gland and deiodinated in the periphery to produce 3,5,3'-tri-iodothyronine (T_3) and 3,3',5'-tri-iodothyronine (reverse T_3). Only T_3 is hormonally active. TRH–thyrotropin-releasing hormone.

replacement and is indicated for the treatment of myxedema coma (TrioStat; SmithKline Beecham, Philadelphia, PA). Its current use in cardiac surgery, sepsis, and other clinical situations is investigational. Additionally, it should be noted that a number of drugs interfere with normal thyroid hormone metabolism; of particular note to cardiac surgeons and cardiologists, amiodarone may induce both hypothyroidism (by blocking nuclear T_3 receptors) and hyperthyroidism (by providing excess inorganic iodine).

Hemodynamic consequences of hyperthyroidism and hypothyroidism

The hemodynamic abnormalities associated with chronic hypothyroidism and hyperthyroidism are well recognized and highlight the importance of normal thyroid function as it relates to the cardiovascular system. Thyroid hormone affects intrinsic myocardial contractility, the peripheral vasculature, and the autonomic nervous system [2,4,5]. Chronic hypothyroid and hyperthyroid states have generally opposing hemodynamic effects; hypothyroidism is associated with impairment of ventricular contractility, an elevation of systemic vascular resistance and decreased heart rate, whereas hyperthyroidism is characterized by a hyperdynamic state manifested by increased cardiac output, lowered systemic vascular resistance, and increased heart rate [6,7]. In extreme cases of hypothyroidism, parenteral T_3 supplementation is effective in reversing the hemodynamic collapse associated with myxedema coma [8]. Diastolic dysfunction, particularly the active component of isovolumic relaxation, is also depressed with chronic hypothyroidism [9]. These profound disturbances in cardiovascular function with chronic thyroid disease provide a rationale for the investigation of the cardiovascular effects of acute disturbances in thyroid metabolism that occur in patients with nonthyroidal disease.

The euthyroid sick syndrome and cardiopulmonary bypass

Although chronic hypothyroidism has long been recognized to adversely affect the cardiovascular system, the recognition that acute disorders of thyroid metabolism

Table 1

Clinical conditions associated with the euthyroid sick syndrome

Sepsis
Brain death
Burn injury
Starvation
Multisystem trauma
Cardiopulmonary bypass
Myocardial infarction
Congestive heart failure

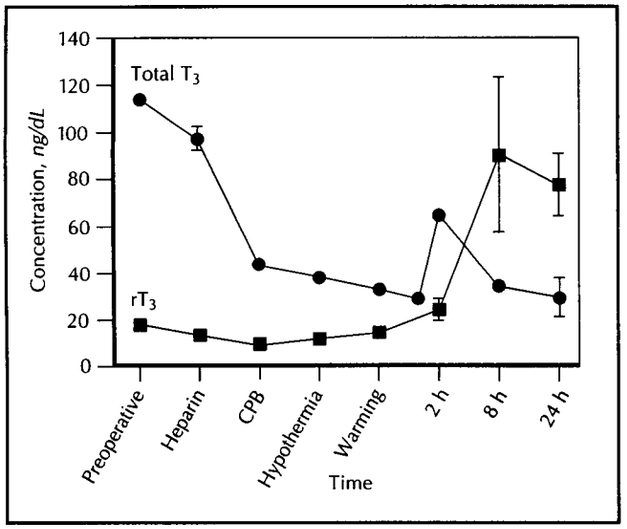

Fig. 2. Effect of cardiopulmonary bypass on circulating tri-iodothyronine (T_3) and reverse T_3 (rT_3). Cardiopulmonary bypass (CPB) induces a functional hypothyroid state, resulting in a significant reduction of circulating and elevated levels of rT_3. (*From* Clark [37]; with permission.)

may be detrimental is relatively recent. Wartofsky and Burman [10] in 1982 used the term *euthyroid sick* to describe the disturbances in thyroid metabolism associated with nonthyroidal illness. The euthyroid sick syndrome is manifested by abnormalities in circulating thyroid hormone levels: namely, low levels of free T_3, normal or high levels of thyronine and high levels of reverse T_3, the inactive metabolite. Since that time, it has become recognized that acute abnormalities of thyroid metabolism are one manifestation of the stress response, along with complement activation, cytokine production, and the release of other inflammatory mediators and can be initiated by a number of diverse clinical conditions (Table 1).

The euthyroid sick syndrome is classically seen in periods of prolonged illness or starvation and may occur in up to 70% of patients in medical intensive care units. Although recognized as a predictor of mortality [11], the functional consequences of the euthyroid sick syndrome are incompletely understood. Whether the euthyroid sick syndrome is pathologic, serves as a marker of severity of illness, or is an adaptive response to severe injury at a time of organism vulnerability is unclear.

In 1978, Bremner *et al.* [12] reported an acute fall in free T_3 levels associated with the initiation of cardiopulmonary bypass in patients undergoing routine cardiac surgery. It has since become recognized that cardiopulmonary bypass initiates a systemic stress response similar to that seen in sepsis and other critical illnessess [13,14]. The low T_3 syndrome after cardiopulmonary bypass first described by Bremner *et al.* has been confirmed and extended by other investigators [15–18] although not universally [19]. The results reported by Holland *et al.* [18] are typical: cardiopulmonary bypass leads to a 75% reduction in free T_3 levels and a threefold increase in reverse T_3 levels that persists in patients up to 24 hours after surgery and perhaps longer (Fig. 2). Accompanying this decrease in T_3 levels, thyroid-stimulating hormone increases, whereas thyronine levels change insignificantly. This low T_3 state in cardiac surgery is chemically identical to the euthyroid sick syndrome seen in nonsurgical patients described by Wartofsky and Burman [10].

Tri-iodothyronine supplementation and the euthyroid sick syndrome

Experimental evidence of hemodynamic benefit

The hypothesis that T_3 supplementation improves contractility after ischemic injury has been upheld in a number of different experimental models, including the isolated rabbit and rat heart [20,21], an *in vivo* porcine model [22], an *ex vivo* canine model [23•], isolated papillary muscle [24], and the isolated porcine myocyte [25]. In each of these preparations, hearts were exposed to a T_3-depleted environment and subjected to ischemic injury; under these conditions, T_3 supplementation significantly improved postischemic left ventricular and myocardial performance.

The mechanism for the improvement in ventricular function with T_3 supplementation after ischemic injury has been the focus of numerous recent studies. Classically, T_3 acts by binding to specific nuclear receptors, initiating gene expression of a number of thyroid-responsive genes. For example, T_3 supplementation alters myosin isoform expression, with a conversion of the V_3 to V_1 isoform, resulting in increased velocity of contraction; additionally,

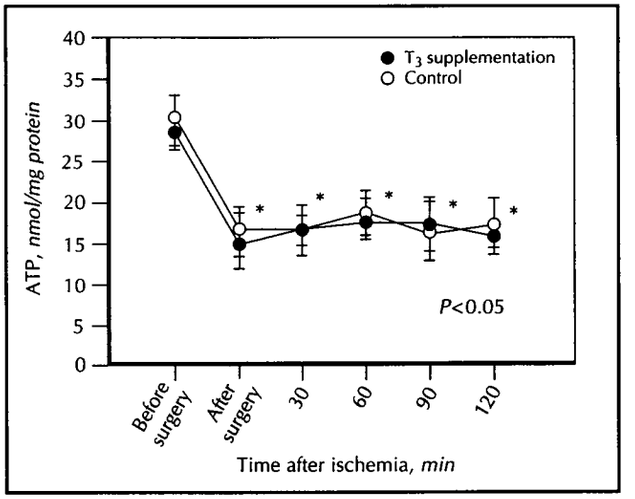

Fig. 3. Myocardial ATP levels after ischemia. Tri-iodothyronine (T_3) supplementation had no affect on myocardial ATP levels or metabolism after global ischemic injury. It is unlikely that the enhanced mechanical performance seen with T_3 supplementation is a result of an increase in myocardial aerobic capacity. (From Dyke *et al.* [22]; with permission.)

T_3 binding affects transcription of the sarcoplasmic reticulum Ca^{2+}ATPase moeity [2]. These and other cardiac proteins (such as the Na^+-K^+ATPase, cytosolic malic enzyme, and atrial natrutetic peptide) are all affected by T_3 binding through nuclear-mediated, transcriptionally based events [2].

In earlier experiments Novitsky *et al.* [26] hypothesised that T_3 supplementation enhanced the aerobic capacity of the heart, increasing myocardial high-energy phosphates available for contraction. These findings have not been confirmed, although T_3 has been demonstrated to affect mitochondrial respiration in vivo [27]. Rather, Dyke *et al.* [22] reported that after global ischemic injury, myocardial ATP levels decreased 50% in a group of animals treated with T_3 (Fig. 3), and that these changes and changes in other ATP metabolites were not different from a similar group of control subjects. It is unlikely that enhanced aerobic metabolism and increased ATP stores can account for the functional improvements seen with T_3 supplementation.

The effect of T_3 supplementation on myocardial contractility after ischemia appears to be rapid in onset, occurring within minutes of drug delivery [20–25]. This nearly immediate contractile response to T_3 supplementation in a variety of models effectively rules out the classic, nuclear-mediated pathway of thyroid hormone interaction as the mechanism for increased contractility after ischemia, as gene stimulation and expression typically takes more time (hours). Thyroid hormone does have potent nonnuclear effects, however, that may rapidly affect myocardial contractility and that are of particular relevance to cardiac surgery and the postischemic heart [28]. Most prominently, T_3 has been demonstrated to affect calcium handling of the myocyte [29,30], which is integral in the pathophysiology of myocardial stunning and postischemic mechanical function [31•,32]. Using an isolated myocyte model, Walker *et al.* [33] recently demonstrated that T_3 supplementation shifts the voltage at peak current of the L-type calcium channel on the sarcolemmal membrane, which regulates calcium release from the sarcoplasmic reticulum. Additionally, they found a synergistic effect between T_3 and β-adrenergic stimulation that resulted in increased cAMP levels and intracellular calcium concentration in their model.

Because chronic hyperthyroidism has been demonstrated to increase myocardial oxygen consumption as well as contractility [34], the effect of acute T_3 supplementation on myocardial energetics is particularly relevant. Klemperer *et al.* [23•] found that acute T_3 supplementation increased contractility without shifting the slope of the relationship of the pressure-volume area to myocardial oxygen consumption, implying that T_3 supplementation improved postischemic ventricular function without incurring the oxygen-wasting debt that occurs with β-adrenergic stimulation. In their study, T_3 supplementation significantly increased coronary blood flow, acting as a coronary vasodilator to match the energy demands induced by the increased contractile performance. Additionally, the authors found that T_3 supplementation to normal, uninjured myocardium did not increase contractility, confirming earlier reports [20]. In this respect, T_3 is similar to milrinone, a phosphodiesterase inhibitor that has also been reported to exert an inotropic effect only after myocardial ischemia and reperfusion [35]. Interestingly, milrinone has a double-ringed structure that resembles the configuration of thyroid hormone and also stimulates calcium ATPase (as well as inhibiting phosphodiesterase III) [36].

Tri-iodothyronine supplementation in cardiac surgery

The rationale for correction of the low T_3 syndrome associated with cardiopulmonary bypass is clear when one considers the hemodynamic consequences of hypothyroidism. Additionally, transient left ventricular dysfunction and hemodynamic lability can be problematic after cardiac surgery, even in patients with preserved ventricu-

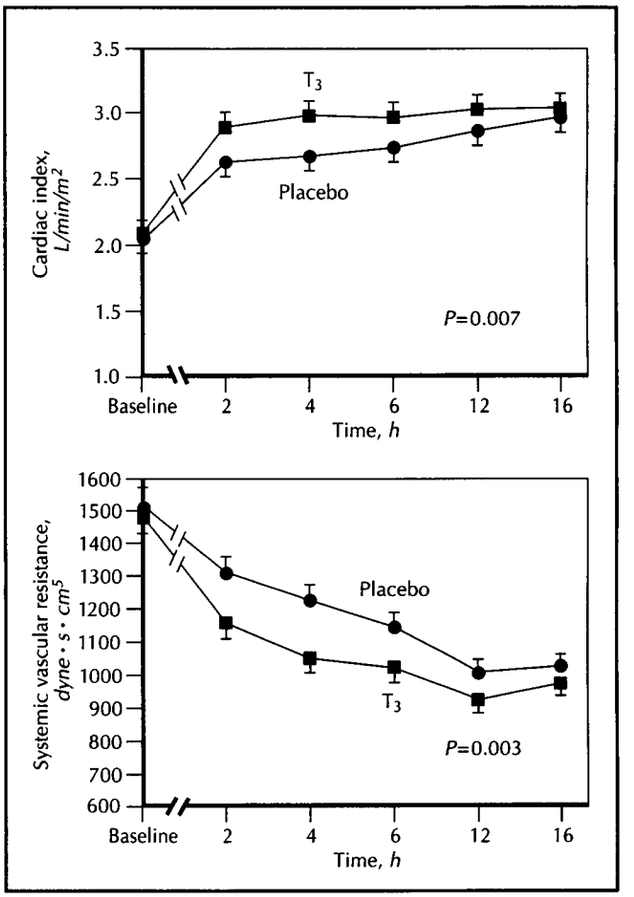

Fig. 4. Effect of tri-iodothyronine (T_3) supplementation on cardiac index and systemic vascular resistance. In a randomized, double-blind trial, T_3 supplementation in patients resulted in a significantly improved hemodynamic profile after cardiac surgery. (From Klemperer *et al.* [48••]; with permission.)

lar function [37]. These factors must be weighed, however, against evidence that correction of the euthyroid sick syndrome has not been demonstrated to be efficacious or improve outcome in other disease states [38], and that T_3 supplementation after cardiac surgery may have other systemic consequences related to oxygen consumption and energy expenditures that are incompletely understood.

The field of organ transplantation was one of the first areas in which T_3 supplementation was used in an attempt to improve cardiac performance by correcting the low T_3 state. Brain death is recognized to severely affect circulating levels of a variety of hormones, including T_3, cortisol, antidiuretic hormone, and insulin [39]. T_3 supplementation has been demonstrated to result in hemodynamic stabilization and improved organ performance after transplantation in a number of experimental models [40–42]. These findings have been extended into clinical trials, in which thyroid hormone supplementation to potential organ donors led to hemodynamic stabilization and a decreased need for inotropic support, resulting in an increased yield of organs for donation [43,44]. Thyroid hormone supplementation remains a standard component of organ donor management in many, but not all, organ procurement organizations in the United States today.

The extension of T_3 supplementation to other areas of cardiac surgery was initiated by Novitsky *et al.* [17,45–47] in the late 1980s. Initially focusing on high-risk patients, they published a series of experimental and clinical articles that suggested that T_3 supplementation was beneficial in assisting the impaired ventricle and salvaging the failing heart after cardiac surgery. These studies confirmed the low T_3 state associated with cardiopulmonary bypass and seemed to demonstrate an improvement in cardiac performance with T_3 supplementation. However, although provocative, many of these studies were limited by the use of heavily load-dependent indices for the assessment of ventricular function and by the lack of a rigorous control population.

Recently, Klemperer *et al.* [48••] published the results of a double-blind, placebo-controlled prospective study of the use of T_3 supplementation in patients with impaired ventricular function undergoing coronary artery bypass grafting. One hundred forty-two patients were recruited to receive either tri-iodothyronine or placebo. T_3 was given at the time of cross-clamp release (0.8 μg/kg), followed by a continuous infusion of 0.113 μg/kg for a total of 6 hours. The infusion was then weaned over 3 hours and stopped. Circulating T_3 levels were significantly reduced after cardiopulmonary bypass in both groups; T_3 levels returned to normal in the supplemented group, and remained low in the placebo group. T_3 demonstrated significant vasoactive effects in the immediate postoperative period. Cardiac index was significantly higher in the treated group up to 12 hours postoperatively (Fig. 4). Similarly, systemic vascular resistance was significantly reduced over the same time frame. The clinical benefit of these hemodyanmic effects was not readily demonstrable, however, as both groups had a similar postoperative course. Morbidity, mortality, and inotropic requirements were not different between groups. This prompted the authors to state that "although tri-iodothyronine improved postoperative cardiovascular performance, we found no decrease in the requirements for traditional inotropic support. Therefore our findings do not support the use of tri-iodothyronine as a substitute for standard drug therapy" [48••].

In a second report from the same study, Klemperer *et al.* [49] also noted that the incidence of atrial fibrillation after coronary artery bypass grafting was significantly reduced in the group of patients receiving T_3 supplementation compared to placebo (24% vs 46%; P=0.009). This difference was evident on the 2nd to 4th postoperative day; there was no difference in the incidence of atrial arrythmias in the immediate postoperative period. The mechanism of this observation is unclear, as is the cause of atrial arrythmias after cardiac surgery in general. However, the authors speculate that a T_3-related attenuation in atrial ischemia-reperfusion injury from an as yet unclear mechanism may be contributory. Additionally, the time course of the finding also makes possible a nuclear-mediated, transcriptionally based mechanism, perhaps relating to plasma membrane and sarcolemmal ion channels [50].

In a well-designed clinical trial, Klemperer *et al.* [48••] demonstrated that T_3 supplementation was safe and effective in improving hemodynamics postoperatively. Although they recommended against its routine use, their study may not have been large enough to adequately identify the subset of patients who might benefit from the improved hemodynamics afforded by T_3 supplementation. Additionally, the possible beneficial effect of T_3 supplementation on postoperative atrial arrythmias deserves further investigation and confirmation, because atrial arrythmias, although usually benign, do have an associated morbidity, as well as prolonging the length of hospitalization and increasing costs [51].

Conclusions

The role of perioperative T_3 supplementation in cardiac surgery is evolving. Although it is unlikely to improve the already good results of cardiac surgery in low-risk patients, reversal of the low T_3 state of cardiopulmonary bypass may be beneficial in patients with severely impaired ventricular function or acutely ischemic myocardium. Clinical studies using more sensitive physiologic endpoints, such as pressure-volume loop analysis, may help identify those patients who may benefit from the use of an old drug in new ways.

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