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Thyroid Hormone Therapy for the Cardiac Surgical Patient

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1. Introduction

Thyroid hormones (THs) are key regulators of metabolism. The thyroid gland produces both thyroxine (T4) and triiodothyronine (T3). T4 is the main product and is converted in the periphery via deiodination to T3 which is the main biologically active TH. The production of THs is regulated by thyrotrophin (TSH) in response to TSH releasing hormone (TRH). This, in turn, is regulated by a negative feedback mechanism related to serum levels of free T3 and T4 (fT3 and fT4). Binding of T3 to TH receptors (TR) followed by binding of T3-TR complex to thyroid response elements within TH responsive genes leads to changes in gene transcription. These effects of TH are present through a wide number of tissues and organ systems including the cardiovascular system.

2. Thyroid hormone and its actions on the cardiovascular system

The effects of TH on both the heart and peripheral vascular system have been well documented[1-9]. In states of TH excess (hyperthyroidism) a high cardiac output state secondary to increased heart rate and contractility with a reduction in systemic vascular resistance (SVR) is seen. In hypothyroidism, the reciprocal effects are observed. The reduction that is seen in SVR is an early response to TH administration[10, 11]. This may be partly due to the release of local vasodilators liberated as a result of increasing metabolic activity and oxygen consumption. The effects of TH on vascular tone may also be attributable to its direct effects on arteriolar smooth muscle. Intracoronary administration of TH in Langendorff preparations has been demonstrated to lead to coronary vasodilatation within 15 seconds[12] and in normal human subjects reductions in SVR are seen within minutes of administration[11], with this effect lasting for several hours when administered intra-operatively[13].

TH is able to manifest its effects on the cardiovascular system at both a genomic and non-genomic level; this means that with administration of TH there are immediate non-genomic cardiovascular consequences[6, 11, 14], followed by later genomic alterations which include alterations in the expression of the beta one adrenergic receptor (ADRB1). However, despite increasing receptor expression, there is a paucity of evidence that T3

administration increases sensitivity to catecholamines[15, 16]. TH also acts upon the expression of calcium handling proteins within the myocyte including the sarcoplasmic reticulum calcium ATPase (SERCA) and its negative regulator phospholamban (PLB). Administration of T3 increases the level of SERCA mRNA and protein and also lowers phospholamban levels and increases its phosphorylation state, which enhances the activity of SERCA[17-22]. The combined effect of these changes is an increase in the force of contraction and speed of diastolic relaxation.

3. The consequences of the hypo-and hyperthyroid states

Hypothyroid patients may have symptoms or signs associated with heart failure including dyspnoea, oedema, cardiomegaly and effusions. Low cardiac output in these patients is due to decreased heart rate, reduced ventricular filling and decreased myocardial contractility. Hypothyroidism is a risk factor for coronary artery disease[23], the incidence of angina and myocardial infarction is however lower and this may relate to a reduction in metabolic requirements of the myocardium. Hypothyroidism is associated with hypertension, secondary to alterations in peripheral vascular resistance. Prolongation of the cardiac action potential and QT interval are also noted [24] and this leads to an increased risk of ventricular arrhythmias in this group. Supplementation with TH can lead to a reversal of some of these cardiovascular manifestations[25]. However, in the setting of cardiac surgery post-operative reductions in circulating THs have been demonstrated to be associated with an increase in the occurrence of atrial fibrillation[26, 27]. The vast majority of patients who are hypothyroid are receiving hormone replacement therapy and are therefore euthyroid at the time of surgery. However, in theory, in the untreated hypothyroid patient acute TH replacement could worsen myocardial ischaemia if myocardial oxygen consumption were increased in the face of fixed oxygen delivery[28]. Surgery in the hypothyroid patient may be performed without increased risk. In patients with untreated mild to moderate hypothyroidism undergoing cardiac surgery, Drucker reported no adverse effects[29] and Syed et al. reported no increase in complications in patients with known hypothyroidism on treatment who were biochemically hypothyroid over those that were biochemically euthyroid without utilising additional TH replacement therapy[30]. O'Connor et al[31] in undiagnosed patients with hypothyroidism have reported the occurrence of severe myxoedema post cardiac surgery leading to significant haemodynamic compromise which recovered with replacement TH therapy.

Hyperthyroid patients commonly have a resting tachycardia. The most common rhythm disturbances are supraventricular arrhythmias including atrial fibrillation which predispose to thromboembolic diseases. Cardiac output may be supranormal (between 50-300% higher than in normal subjects). This is secondary to increases in heart rate, left ventricular contractility, blood volume and a reduction in SVR[8]. Improvements in LV systolic and diastolic function are believed to be modulated by changes in the expression of contractile and calcium regulating proteins (SERCA and PLB). Even though cardiac output is high it may be suboptimal at times of exertion[32], due to an inability to further augment heart rate or lower systemic vascular resistance. Long-term follow-up of patients with hyperthyroidism reveals an increased cardiovascular and cerebrovascular mortality. This may partially be related to the increased rate of supraventricular dysrhythmias[33,34]. In the setting of overt clinical and biochemical hyperthyroidism surgery should be deferred if possible, until the patient can be rendered euthyroid in order to avoid thyroid storm.

4. The non-thyroidal illness syndrome

In response to severe physiological stress including cardiac surgery, changes in circulating concentrations of T3, T4 and TSH occur. The term non-thyroidal illness syndrome (NTIS) has been used to describe this phenomenon as it makes no presumption regarding the metabolic state of the patient. Whether hormone supplementation to correct these abnormalities is beneficial or not is unproven and much debated[35]. There are a variety of mechanisms that could potentially explain the biochemical profile observed in the NTIS including modifications of the hypothalamic-pituitary-thyroid axis, altered binding of TH to circulating proteins, modified entry of TH into tissues, changes in TH metabolism due to modification of the iodothyronines deiodinases as well as changes in TH receptor expression or function[36]. Circulating levels of T3 decrease within two hours of severe physiological stress and this is thought to reflect a reduction in the peripheral conversion of T4 to T3[37, 38]. The most common abnormality observed in severely ill hospitalised patients is a low T3 syndrome, which occurs in up to 70% of patients[39]. Reduction in concentrations of free T3 (fT3) in hospitalised patients have been demonstrated to be predictive of mortality[40]. Deficiencies in TH metabolism have also been demonstrated to occur at a tissue level with a positive correlation between circulating and tissue TH levels[41]. As T3 levels fall reverse T3 (rT3, an inactive metabolite) increases. With increasing severity of illness, T4 levels also begin to fall (low T3-low T4 syndrome). Whether these observed responses are energy conserving to reduce metabolic rate or pathological requiring TH supplementation still remains a matter of debate.

5. The effects of cardiopulmonary bypass on circulating levels of thyroid hormone

With the stress response associated with surgery, concentrations of fT3 are noted with a more precipitous decline following institution of cardiopulmonary bypass (CPB). These further reductions may relate either to a secondary increase in the stress response or to haemodilution[42]. Occurrence of the NTIS has been well documented in the context of both adult and paediatric cardiac surgery[13, 43, 44]. Supplementation with both oral and intravenous T3 has been demonstrated to raise circulating T3 levels to normal or supra-normal levels[13, 45].

It was believed that occurrence of NTIS may be related to the stress response and haemodilution associated with CPB. However, data from patients undergoing cardiac surgery without CPB have demonstrated that the reductions in T3 that have previously been observed in trials of patients undergoing cardiac surgery utilising CPB also occur in the off-pump group to a similar magnitude. This implies that the NTIS during cardiac surgery is a non-specific stress response and CPB is not the only contributing factor to its occurrence[46, 47].

6. The rationale for treatment of the NTIS in patients undergoing cardiac surgery

If the NTIS is truly a maladaptive phenomenon, therapy with TH supplementation may have potentially beneficial effects by rectifying the observed abnormalities and increasing myocardial performance via both genomic and non-genomic mechanisms, thereby having the potential to improve patient outcomes.

In addition to the beneficial haemodynamic effects seen with T3 administration, there is a mounting body of both animal and clinical data suggesting that T3 may have a positive influence on protecting the myocyte following ischaemia. Two weeks administration of T4, followed by ischaemia and reperfusion in an isolated rodent heart model has been

demonstrated to improve post-ischaemic function in T4 treated hearts with attenuation of activation of the p38 mitogen activated protein kinase (MAPK)[48]. In a murine coronary artery ligation model of acute myocardial ischaemia, animals administered T3 demonstrated improved haemodynamic function as well as reducing ischaemia induced apoptosis with an associated increase in Akt signalling compared with placebo[49]. In addition, following a period of global ischaemia in a rodent isolated heart model, T3 administered at reperfusion led to a reduction in apoptotic damage with reduced caspase-3 activity and activated p38 MAPK after one hour of reperfusion. These effects were associated with improved recovery of post-ischaemic function when compared to control hearts[50]. In patients undergoing isolated coronary artery bypass graft surgery (CABG) administration of T3 at reperfusion and for six hours after has been demonstrated to improve haemodynamic function in the immediate post-operative period with an associated reduction in the release of troponin I compared with placebo therapy[51].

7. Development of the use of thyroid hormone as an inotropic agent during cardiac surgery

The salutary effects of acute T3 supplementation have previously been demonstrated in a number of animal models that aimed to recreate the post-ischaemic dysfunction observed after cardiac surgery.

Novitzky demonstrated in both a porcine and canine models of ischaemia-reperfusion that T3 administration was able to attenuate the post-ischaemic left ventricular dysfunction compared with control[52, 53]. In isolated canine hearts subjected to hyperkalaemic arrest, Klemperer demonstrated that T3 supplementation following reperfusion led to an increase in preload recruitable stroke work area. This occurred without an increase in myocardial oxygen consumption, suggesting that administration of T3 in patients with a myocardial oxygen debt does not exacerbate this debt[54].

8. Thyroid hormone supplementation in paediatric cardiac surgery

There are a number of randomised controlled trials of T3 supplementation in paediatric cardiac surgery. These studies have been mainly performed in heterogeneous groups of patients with a variety of CPB and temperature management strategies, age ranges and diagnoses.

During paediatric cardiac surgery, Murzi et al. noted a significant reduction in fT3 with a nadir at 48 hours post-operatively and levels still below baseline values up to six days post-operatively. Levels of fT4 were reduced at six hours with a nadir at 72 hours, however, the magnitude of the decline was not as great as that seen with fT3[43]. Saatvedt et al. demonstrated in a population of paediatric cardiac surgical patients a reduction in fT3 and TSH with an increase in fT4 in the first 48 hours following surgery[55]. They attributed the increase in fT4 to the competition with free fatty acids (which are liberated by systemic heparinisation) in binding to plasma proteins, thus increasing fT4 levels. Marks et al demonstrated a reduction in TSH to lower limits of normal and reduced fT4 total T3 and fT3 index to below normal ranges and correlations between increased intensive care unit stay and mechanical ventilation to the degree of NTIS was observed[44].

Bettendorf et al conducted a randomised double-blind placebo controlled trial of 40 paediatric patients randomised to receive either T3 ($2\mu g.kg^{-1}$ on the first post-operative day,

followed by 1μg.kg^{-1} on subsequent days) or placebo for up to 12 days following surgery. T3 therapy led to significantly higher serum circulating TH levels and the mean change in cardiac index was significantly higher in those that received T3 (20.4% vs. 10.0%, p=0.004). A sub group of patients with increased operative and CPB times were demonstrated to have improvements in systolic function measured by transthoracic echocardiography for T3 treated patients. The level of post-operative inotropic support was not different between groups[56].

In 28 children under seven years of age, Chowdhury et al randomised patients to receive either T3 at an infusion rate of 0.05-0.15μg.kg^{-1}.h^{-1} to maintain serum T3 levels within a normal range or placebo for a maximum of seven days[57].Sub-group analysis of the nine neonatal patients (less than one month) demonstrated a reduction in inotrope and therapeutic intervention scores. No significant difference was noted in the main trial group.

Mackie et al reported on the effects of T3 supplementation (0.05μg.kg^{-1}.h^{-1}) following termination of CPB and continued for a maximum of 48 hours in a randomised double-blind placebo controlled trial (n= 42) on neonates undergoing Norwood repair or repair of interrupted aortic arch with ventricular septal defect. Administration of T3 was noted to be safe but did not improve haemodynamic function. T3 treated patients had a shorter time to negative fluid balance compared with controls[58].

The largest randomised controlled trial to date of T3 supplementation in the paediatric surgical population is the triiodothyronine supplementation in infants and children undergoing cardiopulmonary bypass (TRICC) trial [59]. Portman and colleagues randomised 198 (analysed 193) children less than two years of age. They stratified to account for the heterogeneity of pathologies seen. T3 was administered as boluses of 0.4μg.kg^{-1} prior to CPB, a further 0.4μg.kg^{-1} at reperfusion, followed by three equally timed doses of 0.2μg.kg^{-1} up to nine hours post reperfusion. The safety of T3 administration in this group of patients with complex congenital cardiac defects was noted. In the entire study group, no difference in haemodynamic, inotropic or post-operative outcomes were detected. However, on planned sub-group analysis a reduction in time to extubation, improvements in cardiac function and reduced inotrope requirements were noted for children less than five months of age.

9. Thyroid hormone supplementation in adult cardiac surgery

Novitzky performed two small randomised blinded trials assessing the administration of T3 in patients undergoing CABG. In the first of these, 24 patients with a left ventricular ejection fraction (LVEF) < 30% were administered either placebo or T3 (n= 12) at aortic cross clamp (AXC) removal and at pre-defined intervals post-operatively. Patients treated with T3, demonstrated a reduction in, inotrope and diuretic requirements. In the following study (n= 24) of this series T3 was administered to those patients with an LVEF > 40%. Those patients treated with T3 (n=13) demonstrated a significant increase in cardiac output with an associated reduction in systemic vascular resistance in the first 24 hours following removal of the AXC[60]. Following the encouraging results of these trials and the preceding animal work, a number of larger trials have been performed.

Klemperer et al randomised 142 patients undergoing first time CABG with LVEF < 40% to receive either placebo or T3 therapy[13]. T3 was administered as a bolus of 0.8μg.kg^{-1} at AXC removal followed by an infusion of 0.113μg.kg^{-1}.h^{-1} for six hours post AXC removal. Treatment with T3 led to supra-physiological levels of T3 (and remained significantly higher during T3 treatment compared to placebo) and were associated with haemodynamic

improvements manifest by an increase in cardiac index and reduction in SVR. No statistically significant difference was noted in the requirement of inotropic or vasoconstrictor support during the six hours of T3 therapy following surgery. The incidence of post-operative atrial fibrillation was significantly reduced in the T3 group[61].

Bennett-Guerro et al randomised 211 patients undergoing CABG surgery[62] believed to be at higher risk of requiring post-operative inotropic support (LVEF < 40%, age > 65 years or cardiac re-operation) to receive either T3, dopamine (as a positive control) or placebo. T3 treatment dose was again a 0.8μg kg^{-1} bolus at AXC removal followed by an infusion of 0.12μg $kg^{-1}.h^{-1}$ for six hours, weaned over the next five hours. The dopamine group received 5μg.kg^{-1}.min^{-1} for six hours, weaned over the next six hours. The post-operative low T3 state was prevented with T3 administration, however, this study failed to demonstrate any significant difference in post-operative haemodynamic performance or inotrope requirements for patients receiving T3 therapy.

In a third study of patients undergoing CABG, Mullis-Jansson et al randomised 170 patients to receive either T3 1μg kg^{-1} at AXC removal followed by an infusion of 1μg.kg^{-1} for six hours. In this trial, T3 therapy was demonstrated to have a significant haemodynamic benefit with an increase in cardiac index in the 12 hours following removal of the AXC but with no significant reduction in the SVR. The requirement for post-operative inotropic and post-operative mechanical circulatory support was also reduced in patients receiving T3 therapy. Post-operative myocardial injury as measured by biochemical markers and electrocardiographic criteria (assessed by an independent blinded cardiologist) was also reduced for patients receiving T3 therapy[63].

In a randomised trial of metabolic and hormonal therapy in patients undergoing first-time isolated CABG patients receiving T3 were demonstrated to have improved haemodynamic performance, reduced inotrope requirements and release of troponin I was significantly reduced for those patients administered T3 [51]. T3 therapy was administered as per the protocol originally set out in the trial by Klemperer et al[13].

In addition to the studies investigating peri-operative intravenous supplementation, the potential benefits of pre-operative oral administration of T3 have been investigated. Sirlak et al[64] attempted to optimise TH levels in patients undergoing CABG with reduced LVEF (<30%). In this study, patients (n= 80) were randomised to receive either oral T3 therapy 125μg per day for seven days prior to surgery and from the first post-operative day until time of discharge or placebo therapy. At anaesthetic induction patients in the T3 treatment group were demonstrated to have significantly higher levels of serum fT3 and significantly reduced serum levels of TSH and T4. Although both groups had reductions in serum fT3 associated with surgery and institution of CPB, the magnitude of the effect was reduced in patients receiving oral T3 and with post-operative re-institution of T3 a more rapid return to baseline levels was noted. Although no benefit was seen in terms of improvement in haemodynamic performance at baseline between the groups, T3 treated patients had a significant increase in both cardiac index and mixed venous oxygen saturations in the first 24 hours when compared with the placebo group. In addition, inotrope requirements, requirement for mechanical circulatory support and intensive care unit length of stay were reduced for the T3 group[64].

Kaptein and colleagues performed a meta-analysis to investigate the effects of TH therapy on post-operative NTIS in adults, They analysed 14 randomised controlled trials (13 of which were in patients undergoing cardiac surgery)[45]. Patients were divided into low and high dose intravenous T3 groups and oral T3 groups. Patients in the high dose group tended

towards supra-physiological concentrations of T3, whereas those in the low dose group were more physiological. For those patients undergoing CABG, both the low (0.0275-0.0333μg.kg^{-1}.h^{-1} for 14 to 24 hours) and high (0.175-0.333μg.kg^{-1}.h^{-1} for six to nine hours) dose treatment groups demonstrated significantly increased cardiac index at four to six hours in pooled analyses. In the low and high dose treatment groups, serum T3 levels were 90-108% and 241-571% of baseline values respectively. No correlation was noted between cardiac index (percentage of basal) and total T3 dose, implying that there may be no additional benefit on cardiac index with increasing T3 dose. No difference in mortality was noted and there was insufficient data to comment on hospital and intensive care unit stay. The overall conclusions of the meta-analysis were that although cardiac index was increased, further information is required to investigate potential deleterious effects such as an increase in myocardial oxygen consumption[45], although this has not been demonstrated in animal studies[54].

10. Summary

The NTIS is a common occurrence following cardiac surgery in both paediatric and adult populations. Supplementation with T3 leads to supra-normal T3 levels and has been shown in a number of studies to

1. Improve haemodynamic performance
2. Reduce inotrope requirements
3. Reduce the need for mechanical circulatory support
4. Attenuate myocardial injury.

As yet none of these trials has demonstrated a major benefit in terms of a significant reduction in post-operative morbidities and mortality and further work is required to ascertain the optimal dose and timing of administration to maximise the potential benefits of T3 therapy in the post-operative cardiac surgical patient.

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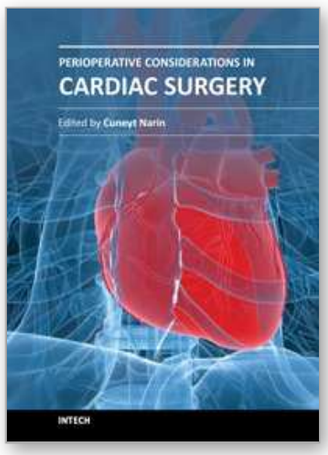

Perioperative Considerations in Cardiac Surgery

Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0147-5
Hard cover, 378 pages
Publisher InTech
Published online 29, February, 2012
Published in print edition February, 2012

This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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