Thyroid hormone and the stunned myocardium

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Abstract

Acute critically ill patients experience a rapid decline in plasma free thyroid hormone levels (free triiodothyronine (FT_3) and free levothyroxine (FT_4)), with a marked elevation of reverse T_3, recognized as the euthyroid sick syndrome (ESS) or low-T_3 syndrome. The ESS is also often associated with depressed myocardial function, sometimes referred to as the 'stunned myocardium'. Its clinical effects may vary from minimal hemodynamic impairment to cardiogenic shock. Medical management may range from aspirin alone to placement of a left ventricular assist device. With adequate supportive therapy, recovery usually occurs within days or weeks. The effect of T_3/T_4 therapy has been studied in three conditions in which the ESS and myocardial functional depression have been documented – i) transient regional myocardial ischemia and reperfusion, ii) transient global myocardial ischemia in patients undergoing cardiac surgery on cardiopulmonary bypass, and iii) transient inadequate global myocardial perfusion in brain-dead potential organ donors. Under all three conditions, myocardial ischemia leads to rapid loss of high-energy phosphates, accumulation of myocardial tissue lactate, and probably loss of homeostasis of cytosolic calcium, which may further increase cell injury. There is an inability to generate ATP through the Krebs cycle, which reduces the high-energy phosphate pool essential for all cell ATPases. Under all three conditions, following administration of T_3/T_4, the myocardial dysfunction was rapidly reversed. We, therefore, cautiously advocate the use of thyroid hormonal therapy to any patient with the ESS and/or a stunned myocardium.

Key Words
- brain death
- cardiopulmonary bypass
- myocardium, stunned
- thyroid hormones

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Introduction: thyroid hormone and the euthyroid sick syndrome

Thyroid hormone production, function, and interaction with other endocrine systems are well understood (Flood *et al.* 2013, Duarte-Guterman *et al.* 2014). Control of the thyroid gland is regulated by hypothalamic and paraventricular nuclei, which release thyroid-releasing hormone directly into the hypothalamic hypophyseal portal venous system, which drains into the anterior pituitary gland, stimulating the release of thyroid-stimulating hormone (TSH), which controls thyroid hormone storage and release (Fliers *et al.* 2006). Most (90%) of the secreted thyroid hormone is tetraiodothyronine (T_4, levothyroxine) and the remaining 10% is triiodothyronine (T_3). These hormones are rapidly bound to proteins, and the amount that remains free in the plasma is small; approximately 5% of T_3 (FT_3) and 10% of T_4 (FT_4) is free (Fliers *et al.* 2006).

T_3 is the active thyroid hormone, and all T_4 secreted by the thyroid gland is converted into T_3 or reverse T_3 (rT_3). Intracellular T_3 has approximately 20 times more potency

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than T_4. Thyroid hormones are essential for proper aerobic mitochondrial function, generation of high-energy phosphates, activation of adenine nucleotide transferase, and prevention of tissue lactic acidosis (Novitzky *et al.* 1988*a*). T_3/T_4 play an important role in intracellular homeostasis of ionized calcium (Straub 2014), thereby avoiding calcium-induced injury (Oshiro *et al.* 2001), mobilizing cytosolic calcium into the sarcoplasmic reticulum, and participating in calcium uptake/calcium release during depolarization/repolarization of myocytes (Zarain-Herzberg & Alvarez-Fernandez 2002). They also play a role in the up-regulation of β adrenergic receptors and protein synthesis. Thyroid hormones affect excitation/contractility coupling and have inotropic properties (Ririe *et al.* 1995), which are dose-dependent (Snow *et al.* 1992), and are strong vasodilators of systemic arteries, including coronary arteries (Klein 2001).

Acute critically ill patients (medical or surgical), who prior to developing the illness/condition were euthyroid and had normal plasma free thyroid hormone levels, experience a rapid decline in FT_3 and FT_4, with a marked elevation of plasma levels of rT_3 (Warner & Beckett 2010). FT_3 plasma levels may fall by 70–90%. The severity of reduction in FT_3/FT_4 has been shown to correlate with patient mortality. TSH levels usually remain within the normal range, though in very sick patients they may be reduced, but not as markedly as FT_3 and FT_4. These acute changes are recognized as the euthyroid sick syndrome (ESS) or low-T_3 syndrome.

Following exposure to an acute pathogenic event (medical, surgical, traumatic), ESS has been observed in the majority of patients admitted to a medical or surgical intensive care unit in practically every acute or chronic stress condition (Table 1). Its cause may be multifactorial. ESS is frequently associated with the presence of high levels of plasma and/or tissue catecholamines (endogenous or exogenous) (Mebis *et al.* 2009), but may also be associated with an inflammatory response. Among multiple markers, tumor necrosis factor-alpha (TNF-α) may participate in the mediation of the ESS. For example, the infusion of TNF-α in humans results in a decrease in serum T_3, T_4, and TSH levels, and a rise in rT_3 (van der Poll *et al.* 1990). The infusion of interleukin-1 (IL1) (Hermus *et al.* 1992), IL6 (Bartalena *et al.* 1994, Stouthard *et al.* 1994), or interferon-alpha (IFN-α) (Corssmit *et al.* 1995) produces a similar effect. As both TNF-α and IL1α can induce the release of IL6, this indicates that IL6 may be the mediator of cytokine-induced changes in thyroid hormones.

ESS is often associated with depressed myocardial function. Inadequate organ perfusion, in turn, precipitates an inflammatory response, with release of oxygen free radicals, which may further compromise myocardial contractility. Multiorgan failure is not unusual (Gou *et al.* 2006). The myocardial dysfunction is usually transient and is sometimes referred to as the 'stunned myocardium'.

Table 1 Conditions in which the euthyroid sick syndrome (ESS) has been described[a]

Acute myocardial infarction, post-cardiac arrest, and low cardiac output related to myocardial dysfunction
Autoimmune diseases
Brain injury and brain death, including brain-dead organ donors
Cardiac surgery on cardiopulmonary bypass
Chronic infection (e.g., cystic fibrosis, tuberculosis, fungal)
Critically-ill ICU patients (from any cause)
Diabetes (uncontrolled, ketoacidosis)
End-stage organ failure, including patients awaiting organ transplantation
Fasting (severe prolonged)
Malignant disease
Sepsis
Shock (hemorrhagic, septic)
Steroid therapy (prolonged)
Trauma

[a]From Novitzky D & Cooper DKC 2013 Thyroid hormone therapy to the recipient of a heart from a brain-dead donor. In *The Brain-Dead Organ Donor: Pathophysiology and Management*, p 322. Eds D Novitzky & DKC Cooper. New York: Springer (with permission).

The stunned myocardium and the ESS

The term 'stunned myocardium' is used in conditions in which the myocardium is depressed following a regional or global ischemic event (Bolling *et al.* 1994, Kloner & Jennings 2001, Luo *et al.* 2010, Heusch 2013). The affected myocardial territory may range from a small volume of myocardial tissue to the entire heart. Its clinical effects may, therefore, vary from minimal hemodynamic impairment to cardiogenic shock. Transient ischemic events may not be severe enough to induce myocyte necrosis, but the myocardium loses its ability to perform work normally. The level of the functional depression is related to the extent of the myocardial ischemia. Its natural course is for recovery to occur within days or possibly weeks. Medical management may range from the administration of aspirin alone to placement of a left ventricular assist device.

Thyroid hormones in the treatment of the ESS

Plasma thyroid hormone values recover once the underlying pathological condition, e.g., pneumonia, myocardial ischemia related to open heart surgery, has been

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reversed. The current consensus, therefore, is that patients exhibiting the ESS should not be subjected to thyroid replacement therapy as it is not believed that the administration of thyroid hormone changes the outcome of the primary disease (Bello *et al*. 2010, Pappa *et al*. 2011).

In our experience, however, the administration of T_3/T_4 has been rewarding in conditions in which myocardial 'stunning' plays a role. These include any condition in which a period of regional or global myocardial ischemia (inadequate blood perfusion) has occurred followed by revascularization and/or reperfusion. In particular, the effect of T_3/T_4 therapy has been studied under three conditions in which the ESS and myocardial functional depression have been documented – i) transient regional myocardial ischemia and reperfusion (Heusch 2013), ii) transient global myocardial ischemia in patients undergoing cardiac surgery on cardiopulmonary bypass (CPB) (Siribaddana 2012), and iii) transient inadequate global myocardial perfusion in brain-dead potential organ donors (Novitzky *et al*. 1984). Under all three conditions, following administration of T_3/T_4, the myocardial dysfunction was rapidly reversed.

We, therefore, suggest that T_3/T_4 therapy may be beneficial not only for these conditions but for any condition that has resulted in a stunned myocardium.

Studies on T_3 therapy in transient regional myocardial ischemia and reperfusion in dogs

Two groups of dogs were subjected to a 15-min period of regional myocardial ischemia by snaring the left anterior descending coronary artery distal to its first diagonal branch (Novitzky *et al*. 1991, Yokoyama *et al*. 1992). After the release of the snare, the dogs were given either placebo or T_3 (0.2 μg/kg) at 30-min intervals.

Plasma FT_3 levels fell significantly during the ischemic period in both groups and continued to fall after reperfusion in the untreated group. In both groups, cardiac function deteriorated significantly during the period of ischemia, but rapidly returned to control levels after reperfusion. After 90 min of reperfusion, however, deterioration of left ventricular function was observed in untreated dogs and was significantly worse than in the T_3-treated dogs, in which hemodynamic function was maintained and, in fact, improved to levels superior to those of controls.

This study indicated that regional myocardial ischemia alone reduces FT_3 levels, and that T_3 therapy might be worthy of a trial in patients with a stunned myocardium in whom reperfusion of the myocardium takes place after variable periods of ischemia.

Studies on T_3 therapy following transient global myocardial ischemia and CPB

A significant reduction in plasma FT_3 has been documented in patients undergoing open heart procedures on CPB (Bremner *et al*. 1978, Robuschi *et al*. 1986, Novitzky *et al*. 1989*a*, Novitzky & Cooper 1990). We proposed the hypothesis that it was this reduction in circulating FT_3 that was in part responsible for a deterioration of myocardial function in such patients.

Studies in pigs and baboons

Twenty-two pigs underwent 2 or 3 h of myocardial ischemia (cross-clamping of the ascending aorta) during CPB at 26 °C (Novitzky *et al*. 1988*b*). The myocardium was protected by a cardioplegic solution and by the local application of cold saline solution. After the pig was rewarmed to 37 °C, CPB was discontinued, and measurements of hemodynamic function were made 10 and 70 min later. Half of the pigs received 6 μg of T_3 i.v. immediately after the removal of the aortic cross-clamp, the remainder receiving no T_3.

After 2 h of ischemia, untreated pigs showed significantly reduced myocardial function 10 min after discontinuation of CPB. By 70 min, two of five untreated pigs had died of low cardiac output, but all five T_3-treated pigs survived. After 3 h of ischemia, both groups showed some reduced function at 10 min, although the reduction was more marked in untreated animals. By 70 min, four of six untreated pigs had died of myocardial failure and all T_3-treated pigs remained alive. Surviving pigs in both groups still demonstrated some reduced function compared with values obtained before CPB.

To clarify the effect of T_3 on myocardial high-energy phosphate stores and lactate, a series of experiments were carried out in baboons undergoing 3 h of myocardial ischemia while supported by CPB (Novitzky *et al*. 1988*c*). At the end of the ischemic period, six received 6 μg of T_3, and seven received no T_3. Seventy minutes after CPB, the myocardial ATP level was significantly higher in the treated animals. In untreated animals, a steady increase in myocardial lactate occurred, and 70 min after CPB was discontinued, there was a significant difference in lactate levels between the two groups.

On the basis of these results, it was postulated that a combination of global ischemia and depletion of FT_3 resulted in reduced mitochondrial function, inhibition of the tricarboxylic acid cycle, inability to utilize oxygen aerobically with resulting increased anaerobic metabolism,

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and depletion of myocardial phosphates. T_3 replacement therapy was presumed to improve mitochondrial function and increase aerobic metabolism, which led to a measured increase in myocardial phosphates.

Studies in patients undergoing open heart surgery on CPB

Initially, we administered T_3 (4–10 μg i.v.) to ten patients, either when difficulty was being experienced in weaning from CPB support ($n=5$) or when myocardial function remained extremely poor, despite inotropic and intra-aortic balloon pump support ($n=5$) (Novitzky *et al.* 1989*b*).

Within 1 h of T_3 administration, the mean plasma free T_3 level had risen from 1.03 to 3.56 μg/ml, and CPB was able to be discontinued in all cases. At 1 h, the mean arterial pressure had risen from 42 to 78 mmHg, and heart rate from 90 to 104 beats/min. The left atrial pressure had fallen from 30 to 14 mmHg, and the central venous pressure from 20 to 11 cm H_2O. All changes were statistically significant. Inotropic support had been significantly reduced or discontinued. Within 3 h, intra-aortic balloon pump support ($n=2$) was no longer essential.

To the best of our knowledge, T_3 had not been administered previously as an inotropic agent to patients who had undergone cardiac surgery. Although this small trial was not randomized, the results indicated that T_3 could play an important role in the rescue of failing hearts following a period of myocardial ischemia in patients who had undergone open heart surgery.

Subsequently, in two small randomized trials in patients undergoing myocardial revascularization on CPB, postoperative T_3 therapy was associated with a reduced need for inotropic support and diuretic therapy (in the first study) and improved cardiac output (in the second study) (Novitzky *et al.* 1989*b*). A later study added support to these observations (Novitzky *et al.* 1996).

Others subsequently continued to study the effects of CPB on thyroid hormones and the effect of thyroid hormones on myocardial function (Dyke *et al.* 1991, Clark 1993, Lowenstein 1993).

Studies on T_3 therapy after brain death

Myocardial stunning has been observed during and following the induction of brain death. This injury occurs at a time of massive release of endogenous catecholamines (Novitzky *et al.* 1984, Shivalkar *et al.* 1993). Electrocardiographic changes correlate well with acute ongoing myocardial ischemia and on occasions mimic an acute myocardial infarction. The catecholamine storm is short-lived, but myocardial injury can be observed under the microscope, and can be prevented by pretreatment with β blockade or calcium antagonists (Novitzky *et al.* 1987*a*).

The surge in catecholamines is associated with rapid declines in plasma levels of T_3, T_4, cortisol, insulin, and antidiuretic hormone (Novitzky *et al.* 1984, 1987*a*, Cooper *et al.* 1989). However, TSH remains within the normal range.

Studies in brain-dead pigs and baboons

The most relevant experiments demonstrated that brain-dead animals were unable to aerobically metabolize radiolabeled metabolites (^{14}C-U-glucose, ^{14}C-1-palmitate, and ^{14}C-1-pyruvate) administered intravenously (Novitzky *et al.* 1988*b*). There was a major change in metabolic oxidative processes. The rate of glucose, pyruvate, and palmitate utilization was markedly reduced, and there was an accumulation of lactate and free fatty acids in the plasma, indicating a change from aerobic to anaerobic metabolism. These metabolic changes were associated with a significant decline in myocardial function. The administration of T_3 to the brain-dead animals resulted in a dramatic increase in the rate of metabolite utilization, and a reduction in the plasma concentrations of plasma lactate and free fatty acids, indicating reversal from anaerobic to aerobic tissue metabolism.

The inability of the brain-dead animal to metabolize cellular fuels aerobically indicates that the mitochondria are no longer functioning and are unable to generate high-energy phosphates; pyruvate does not enter into the mitochondria, but accumulates as lactate (Novitzky *et al.* 1988*b*, Stacpoole 1997). As time post-brain-death progresses, the inhibition of the Krebs cycle becomes greater, and mitochondrial failure leads to i) depletion of high-energy phosphates, ii) tissue lactic acidosis (Sztark *et al.* 2000), iii) loss of cellular homeostasis, iv) inability to maintain ionic ATPase function v) inability to maintain ion compartmentalization, and vi) deactivation of sodium/potassium cellular pumps. Increments of cytosolic calcium uptake no longer occur, and calcium is released from the sarcoplasmic reticulum into the cytosol, eventually resulting in cell death.

These results indicated that T_3 should be administered to all brain-dead potential organ donors to correct and maintain a more physiological metabolic status and thus improve organ function.

Studies in human brain-dead potential organ donors

Following brain death, recovery of myocardial perfusion results in a degree of recovery, and the heart may continue

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beating well, while it remains in the vasodilated donor (where peripheral vascular resistance is low). The further period of ischemia while the donor heart is transported and transplanted may lead to further stunning and poor prolonged myocardial depression.

Hormonal therapy that included T_3 was first administered to a series of brain-dead potential organ donors at Groote Schuur Hospital at the University of Cape Town in 1984 (Novitzky *et al.* 1986, 1987*b*, Cooper *et al.* 1989). The initial regimen involved the hourly administration of T_3 (2 μg), cortisol (100 mg), and insulin (20 units).

Twenty-six conventionally treated donors (with no hormonal replacement therapy) showed abnormal electrocardiograms (resembling myocardial ischemia), progressive hemodynamic deterioration requiring significantly increased inotropic support to maintain hemodynamic stability, and progressive lactic acidosis requiring frequent bicarbonate administration to maintain a normal acid–base balance (Novitzky *et al.* 1987*b*). Of this group, five (19%) of the donors were considered unsuitable as cardiac donors due to progressive cardiovascular deterioration or sudden ventricular fibrillation. Hormonal replacement therapy was administered to 21 donors, resulting in normalization of the electrocardiographic abnormalities, significant improvement in hemodynamic status, reduced inotropic support, and reduced requirement for bicarbonate. In these donors, all organs were acceptable for transplantation, which was followed by excellent organ function in the recipients.

Thyroid hormone therapy of the brain-dead potential organ donors remained controversial for many years and is still not universally administered (Macdonald *et al.* 2012, Rech *et al.* 2013). We have, therefore, recently reviewed data provided by the United Network for Organ Sharing (UNOS) on hormonal resuscitation therapy in the management of 63 593 brain-dead potential organ donors in the USA in the 10-year period 2000–2009 (Novitzky *et al.* 2014). There was a clear benefit in terms of the number of organs that could be procured (and transplanted) from donors that received T_3/T_4 when compared with those that did not, representing an increase in organs procured of 12.8% ($P<0.0001$).

In a cohort of 40 124 donors in which details of all hormonal therapy were available, there was a clearly increased procurement/transplantation rate for the heart, lung, kidney, pancreas, and intestine when T_3/T_4 had been administered. There was no overall benefit of T_3/T_4 on liver procurement, although one subgroup showed a significantly higher procurement rate when T_3/T_4 was administered, and in the other subgroups there was no detrimental effect.

Thyroid hormone therapy: potential mechanisms

All of the conditions described above demonstrate variable degrees of myocardial stunning. The myocardial ischemia leads to rapid loss of high-energy phosphates, accumulation of myocardial tissue lactate, and probably loss of homeostasis of cytosolic calcium, which may further increase cell injury. There may also be mitochondrial injury, which varies in degree. There is an inability to generate ATP through the Krebs cycle, which reduces the high-energy phosphate pool essential for all cell ATPases.

Total nucleotides may remain reduced for several days, as there is a relatively slow process of *de novo* synthesis. The mechanism of action of the thyroid hormones has been discussed previously (Song *et al.* 2007, Shapiro & Baron 2013) and will not be considered in detail here. In summary, these hormones appear essential for reactivation of mitochondrial energy metabolism (in the Krebs cycle), and this contributes to hemodynamic stability. T_3 may facilitate recovery of the stunned myocardium by increasing ATP, and by activating the adenyl nucleotide transferase, enhancing the transfer of ATP from the mitochondria into the cytosol. Exogenous T_3 may have an effect on the cytosolic ATPases, affecting ATP-dependent ionic pumps, such as the calcium pumps, and calcium is rapidly mobilized in the sarcoplasmic reticulum.

For example, brain-dead organ donors suffer from various degrees of deprivation of high-energy phosphates and, as time passes, there is a progressive accumulation of tissue and plasma lactate, which, despite bicarbonate replacement, leads to progressive acidosis. These donors progressively become refractory to exogenous catecholamines and are eventually lost from the donor pool due to hemodynamic instability. The pathophysiology of brain death and the mechanisms by which hormonal therapy may improve donor organ function have recently been comprehensively reviewed (Novitzky & Cooper 2013).

The mechanisms related to the beneficial effects of thyroid hormone on the stunned myocardium have been investigated by several groups, but particularly by Pantos & Mourouzis (2014). Once thought to be detrimental to the ischemic myocardium, thyroid hormones are now recognized to have anti-ischemic and inotropic actions. Indeed, they can protect against the detrimental effects of inotropic agents that exacerbate post-ischemic myocardial dysfunction (Pantos *et al.* 2003*a*). However, in addition to their action on metabolism and calcium handling, there is increasing evidence of their effect on stress-induced intracellular signaling, in part related to inhibition of apoptosis,

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mediated through thyroid hormone receptor α1 (Pantos *et al*. 2009, 2011, Pantos & Mourouzis 2014). This may explain why T_3 is more effective than T_4 (Pantos *et al*. 2009, 2011, Pantos & Mourouzis 2014). Thyroid hormone enhances the activation of Akt signaling, which is essential for mitochondrial function (Mourouzis *et al*. 2012, Adamopoulos *et al*. 2013). Furthermore, thyroid hormone increases basal expression and phosphorylation of heat shock protein-27, conferring protection of the myocardium against ischemia–reperfusion injury (Pantos *et al*. 2003*b*).

We, therefore, cautiously advocate the use of thyroid hormonal therapy to any patient with the ESS and/or a stunned myocardium, as also recommended by others (de Groot 2006). In the field of organ transplantation, T_3/T_4 therapy is advocated for the donor and, because the patient undergoing heart transplantation has been supported by a period of CPB (resulting in a low FT_3), we also recommend T_3 therapy for the recipient (Novitzky *et al*. 1988*d*, 1990). By correcting the metabolic derangements that take place in the donor, the heart will be excised with close to normal levels of energy stores that can be utilized during the period of myocardial ischemia, while the heart is transported to the recipient center and transplanted into the recipient. T_3 replacement therapy administered to the recipient, before the removal of the aortic cross-clamp, will lead to rapid restoration of energy stores that may have decreased during CPB, with associated improvement in myocardial function.

In summary, patients who exhibit the ESS (whatever the underlying cause) may experience acute myocardial depression, which may require some type of cardiac support. This may involve inotropic agents, placement of an intra-aortic balloon pump, or even mechanical support of the heart. Thyroid replacement therapy may rapidly reverse this state of myocardial dysfunction, allowing all forms of myocardial support to be discontinued or significantly reduced.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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