Endocrinol Metab Clin N Am
32 (2003) 503–518

ENDOCRINOLOGY
AND METABOLISM
CLINICS OF
NORTH AMERICA

Perioperative management of patients with hypothyroidism

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Effects of hypothyroidism on perioperative parameters

Thyroid hormones have a wide variety of actions in virtually every organ system. They play a crucial role in regulating important functions such as cardiac contractility, vascular tone, water and electrolyte balance, and normal function of the central nervous system. It is now widely accepted that an euthyroid state marked by adequate levels of thyroid hormones is necessary to obtain the best possible results from any kind of surgical intervention.

Effects of hypothyroidism on the cardiovascular system

Arguably the most important adverse effects of hypothyroidism that may predict a bad surgical outcome are those affecting cardiac function. Among many cardiovascular abnormalities described in hypothyroid patients are impaired cardiac contractility with decreased cardiac output, increased peripheral vascular resistance, and decreased blood volume.

Several cardiac parameters indicate depressed myocardial function in hypothyroid patients. Cardiac output decreases by as much as 30% to 50% [1], heart rate decreases slightly, and cardiac contractility is adversely affected with subnormal systolic and diastolic function. Several parameters of the cardiac cycle are influenced by hypothyroidism. The degree of preejection period prolongation and the reduction of left ventricular ejection time correlate directly with the severity of clinical hypothyroidism. A decrease of 60% in the left ventricular ejection time and a prolongation of the preejection period by 40% can be seen in cases of severe hypothyroidism. These changes may be particularly important for the surgical patient with some degree of preexisting heart failure.

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doi:10.1016/S0889-8529(03)00007-0

The molecular changes underlying these abnormalities are believed to be multifactorial. Myxedematous infiltration (glycosaminoglycans) of the myocardial tissues has been documented. Alterations in calcium handling seen in the cytoplasmic reticulum and a depression of the myosin ATP-ase activity contribute to the observed decrease in myocardial contractility [2]. A decrease in the rate of calcium uptake and calcium-dependent ATP hydrolysis has been demonstrated in myocardial sarcoplasmic reticulum of hypothyroid animals [3]. These effects, which can be seen within hours if not minutes, suggest an effect of thyroid hormone on myocytes independent of classic nuclear gene transcription action.

Thyroid hormones influence cardiac function by exerting their effect on several genes in the cardiac myocytes either in a positive (myosin heavy chain, SR-Ca^{2+}, Na^{+}-K^{+}-ATPase, β-adrenergic receptors), or negative fashion (α-myosin heavy chain, T_3 nuclear receptor-1, adenylate cyclase types 5 and 6, phospholamban). There is evidence to suggest that the on-rate or induction of transcription of specific genes by thyroid hormones differs from the off-rate of transcription (following withdrawal of thyroid hormones) with the latter taking more time [4].

An increased peripheral vascular resistance is routinely seen in hypothyroid patients, and this is believed to be due directly to the deficiency in thyroid hormone. T3 seems to exert a vasodilatory effect by a direct action on the smooth muscle of the blood vessels and an effect on endothelial function [5,6]. The decrease in oxygen demand of peripheral tissues associated with hypothyroidism may also play a role in the increase of systemic vascular resistance, which in turn causes an increase in the cardiac afterload. A lowering of the cardiac output follows, because of a decrease of the left ventricular ejection fraction and a small drop of the heart rate. An effect on blood pressure is also seen with an increase in diastolic pressure and a decrease in the systolic pressure. On average, the mean blood pressure remains unchanged although hypertension is not an uncommon finding, and the classic finding of a reduced pulse pressure is also seen.

Loss of the cardiovascular responses to acute increases in intrathoracic pressures is often seen in the setting of hypothyroidism. As such, there is an absence of the usual reflex slowing of heart rate and loss of the compensatory increase in diastolic arterial pressure following a Valsalva maneuver, implying a hypothyroidism-induced baroreceptor defect [7]. This condition may explain in part the tendency of hypothyroid patients to become hypotensive when exposed to anesthetic agents. A complex interaction between thyroid hormones and catecholamines seems to exist. Hypothyroid patients have a depressed adrenergic tone, which is not caused by decreased levels of catecholamines. On the contrary, catecholamine levels are increased and possible explanations for this paradoxical phenomenon include a down-regulation of β-adrenergic receptors, loss of a direct "catecholamine-like" action of thyroid hormone or an increase of intracellular levels of inhibitory guanine nucleotide-binding (G) protein [2].

A variety of electrocardiographic abnormalities have been reported in hypothyroid patients, particularly in the perioperative period. Bradycardia is most commonly observed, but other, more severe abnormalities have also been documented with some frequency, including the ventricular tachyarrhythmia of "torsade de pointe" [8]. The duration of the action potential is thought to be prolonged and possibly caused by an effect of a decreased number of voltage-gated potassium channels (related to down-regulation of the gene expression induced by the decreased levels of thyroid hormone). Other nonspecific changes are also seen on the electrocardiogram of these patients, such as low voltage and nonspecific ST changes, and adequate therapy with thyroid hormone results in resolution of such changes. It should be emphasized that thyroid deficiency is not the only cause of these rhythm disturbances and EKG changes; therefore, a high index of suspicion for other causes must be maintained—especially in patients with previous cardiac history who are undergoing surgical stress.

It is easy for one to imagine how the changes (stated earlier) on the cardiovascular system could adversely affect a patient and predispose to the development of heart failure. Related to associations with hypercholesterolemia, diabetes, and underlying coronary artery disease, hypothyroidism is only rarely documented as a sole cause of heart failure. In assessing the relative role of hypothyroidism in contrast to other factors, it should be noted that differences exist in the way hypothyroid patients respond to various stresses as compared with patients with congestive heart failure (CHF). Hypothyroid patients can increase their cardiac output or decrease their systemic vascular resistance in response to exercise [9]. The tissues of hypothyroid patients have normal or depressed oxygen consumption whereas it is increased in patients with CHF. Hypothyroid patients are also unable to excrete a sodium load, which would induce symptomatic worsening in the presence of CHF [10]. These data suggest that although hypothyroidism may contribute to the worsening of congestive heart failure, it is rarely the major cause.

Other concomitant aspects of the hypothyroid patient may influence cardiovascular function and affect surgical outcomes. Patients with longstanding hypothyroidism typically have elevated cholesterol levels and abnormal coagulation parameters (see later discussion) that may predispose them to cardiovascular events such as myocardial infarction or cerebrovascular accidents in the perioperative period. Several studies have looked at cholesterol levels of hypothyroid patients as compared with euthyroid controls and document a worsening lipid profile with worsening thyroid function [11,12]. A correlation between even mild or "subclinical" hypothyroidism and increased risk for coronary events was documented in the Rotterdam study [13].

Few studies have been reported that have directly assessed the clinical outcomes of hypothyroid patients after various surgical procedures. One interesting, albeit retrospective, study [14] compared the outcome of

euthyroid and hypothyroid patients undergoing percutaneous transluminal coronary angioplasty (PTCA), and also compared the outcome of hypothyroid patients undergoing either PTCA or coronary artery bypass graft (CABG) surgery. There were no differences between the euthyroid and hypothyroid patients undergoing PTCA (outcomes addressed included procedure-related mortality, coronary artery dissection, reocclusion, bradycardia, heart failure, hypotension, and myocardial infarction). There were differences, however, in outcomes between the hypothyroid patients undergoing PTCA and those undergoing CABG. Those having CABG had a higher incidence of heart failure, hyponatremia, gastrointestinal dysfunction, and fever. These data suggest that if hypothyroid patients need a revascularization procedure, PTCA may be a better choice if there is no time to render them euthyroid. The findings must be interpreted cautiously as only suggestive however, because of the retrospective nature of the study, and few hypothyroid patients.

Many studies have examined the potential benefits of thyroid hormone administration on cardiovascular function. Because brain death is associated with an increase of catecholamine levels and an enhanced systemic vascular resistance [15], thyroid hormone has been examined for its ability to lower peripheral resistance and increase blood flow in brain dead organ donors. Animal models first demonstrated an improvement in cardiac function after administration of T3 [16,17], and later reports in humans [18,19] indicated improved function of transplanted hearts if donors were treated with T3 before transplantation. Unfortunately, most of these studies were not randomized or blinded, and well-designed studies are necessary to better assess the application of thyroid hormone therapy to transplantation medicine. Table 1 summarizes the diverse cardiovascular effects of hypothyroidism.

Effects of hypothyroidism on ventilation

Several abnormalities in the respiratory function of hypothyroid patients have been described, such as a decrease in maximal breathing capacity and a diminished diffusing capacity for carbon monoxide. In severe hypothyroidism, hypoxic ventilatory drive can be greatly depressed, showing almost no increase in minute ventilation even at low alveolar oxygen tension. Hypercapneic ventilatory drive is also often severely impaired, although the exact mechanism for these effects is not clear. One of the many factors implicated in the etiology of impaired respiratory function is that of respiratory muscle weakness. Impaired respiratory muscle function is the result of intrinsic changes (as induced by altered gene expression of key gene products in the muscle cells) [20] and dysfunction of the phrenic nerve that innervates them [21]. Most of the available evidence for these abnormalities comes from either animal studies or human studies without adequate controls or numbers of patients. The presence of hypothyroidism with

Table 1
Cardiovascular manifestations of hypothyroidism

Cardiovascular manifestation	Result
Blood pressure	
Systolic	Decreased
Diastolic	Increased
Heart rate	Decreased
Systemic vascular resistance	Increased
Cardiac mass	Decreased
Cardiac contractility	Decreased
Cardiac output	Decreased (as much as 30%–50%)
Congestive heart failure	Increased
Baroreceptor defect	Decreased response to increased intrathoracic pressure
Pericardial effusion	
EKG effects	
Bradycardia	
Arrhythmia	QT interval prolongation
Low voltage	
Lipid effects	
Total cholesterol	Elevated
LDL cholesterol	Elevated
Triglycerides	Elevated

muscular dysfunction together with increased size of the muscles has been called Hoffmann's syndrome [22].

Several reports have associated hypothyroidism with sleep apnea and all its complications, which can adversely influence surgical outcome [23] or make postoperative extubation problematic. In addition to the possible above mechanisms underlying abnormalities in ventilatory drive, direct obstruction to the upper airway may occur related to the increased tongue size seen in hypothyroidism. Whereas obesity may be a factor in some patients, improvement in symptoms with levothyroxine replacement is possible even in the absence of weight loss. Reduced ventilatory excursions related to muscle weakness and obesity may result in atelectasis, reduced lung volumes and reduced exercise capacity. The available evidence on the importance of each of these factors is conflicting with some reports indicating improvement with levothyroxine replacement even in the absence of weight loss whereas others indicate little change in respiratory function with correction of hypothyroidism but some improvement with weight loss. Clearly there is a complex interaction between the two that should be addressed in these patients. Whereas apparently rare, there is one report of a hypothyroid patient with a purely central sleep apnea [24], which is therefore yet another mechanism for hypothyroidism induced sleep apnea. Little is understood about the mechanisms underlying the interaction of thyroid hormones with the respiratory centers of the brain.

Finally, there is evidence to suggest that severe stress, such as sepsis—occasionally seen in the perioperative period—causes decreased surfactant

synthesis and worsening of the respiratory function. Hypothyroid patients have slowed drug metabolism and the addition of pharmaceutical agents that suppress respiratory function (such as sedatives or any of the commonly used anesthetics) can precipitate respiratory failure. In animal models, improvement of surfactant synthesis and improved clinical outcomes have been documented with T3 therapy [25]. The effect of thyroid hormones on surfactant synthesis in humans has best been best studied in neonates at risk for respiratory distress syndrome (RDS). Studies have been conducted in which intraamniotic T3 was administered to premature infants being delivered while still at high risk for RDS [26]. These neonates also had a low lecithin/sphingomyclin amniotic ratio that is an indicator of poor lung compliance and immaturity. Repeat amniocentesis after administration of intraamniotic T3 indicated improved amniotic lipids, and the treated infants did not develop RDS. The causal relationship is not clear because intraamniotic administration of medications can be a stressful procedure that may induce surfactact synthesis (perhaps caused by the increased levels of corticosteroids in response to the stress). Administration of thyroid hormone to the mother is a problem because the degree to which T4 or T3 cross the placenta is not predictable. One hormone of the thyroid axis that readily crosses the placenta is thyrotropin releasing hormone (TRH). Combined maternal therapy with corticosteroids and TRH has been examined in women with infants at high risk for RDS [27]. This treatment resulted in reduced bronchopulmonary dysplasia and the number of ventilator dependent days. Unfortunately, other studies failed to confirm these results [28]. The molecular mechanisms by which thyroid hormone influences surfactant synthesis or function (eg, increased production or increased secretion by type II pneumocytes) remains unclear at this time.

There are reports [29] in the literature indicating that hypothyroid patients tend to be more susceptible to anesthetic agents. The use of tranquilizers, narcotics, and hypnotics should be avoided or reduced to a minimum. There is some experimental data from animal studies indicating that thiobarbiturates may have antithyroid properties, a factor that needs to be taken into account if these agents are used in hypothyroid patients. Table 2 summarizes the many effects of hypothyroidism on the pulmonary system.

Effects of hypothyroidism on renal function and plasma volume

The basis for the decreased plasma volume in hypothyroid patients is multifactorial. The capillary permeability increases and induces a shift of water and albumin into the interstitial space. Another factor is the deposition of glycosaminoglycans in the interstitial tissues (which induces nonpitting edema). These large molecules may have an osmotic effect inducing further shifts of fluids from the intravascular to the extravascular space, resulting in decreased effective plasma volume.

Table 2
Pulmonary effects of hypothyroidism

Pulmonary effect	Result
Ventilatory drive	
Response to hypoxia	Decreased
Response to hypercapnea	Decreased
Respiratory muscle strength	Decreased
Sleep apnea	Increased
Obstructive (macroglossia)	Increased
Obesity related	Increased
Central	Increased?
Lung volumes	Decreased
Atelectasis	Increased
Pneumonia	Increased
Susceptibility to respiratory depressants	Increased
Surfactant synthesis	Decreased?

Hypothyroidism has multiple effects on renal function. These include decreased renal perfusion, increased antidiuretic hormone (ADH), decreased atrial natriuretic factor (ANF), and decreased activity of the renin-angiotensin-aldosterone system. The hyponatremia that is commonly associated with hypothyroidism must be considered in surgical patients who develop worsening renal function in the perioperative period, and its correction is easy and safe. Two recent studies [30,31] followed hypothyroid patients and monitored multiple renal parameters such as blood urea nitrogen (BUN), creatinine, creatinine and BUN clearance (by 24 hour urine collections), weight, presence of edema, serum sodium (Na^+), ADH, ANF, and the renin-angiotensin-aldosterone system before and after therapy with thyroid hormone. These patients had ''normal'' renal function as determined by serum creatinine and BUN. Serum creatinine did not change significantly but BUN, creatinine clearance, and serum sodium (in those who had hyponatremia) improved. Increased levels of ADH and decreased levels of ANF were noted at baseline in the hypothyroid patients as compared with healthy controls, and normalized after treatment with levothyroxine. Increased natriuresis persisted though, which may be a result of improved cardiac function and elevated levels of ANF. At baseline, plasma renin activity and aldosterone levels were similar in hypothyroid and control subjects, whereas a significant increase was noted with treatment. This result may somehow reflect the decreased water clearance by the kidneys in the hypothyroid state, which is corrected with therapy. A kaliuresis was observed at the end of the study that may be explained by an increased aldosterone level.

Worsening renal function is not a rare event in the early postoperative period, often associated with intra-operative hypotension, and this is likely to be a more common phenomenon in the presence of hypothyroidism [32]. There are also cases in the literature of hypothyroidism presenting as chronic renal failure, and resolving completely with restoration of

euthyroidism [33]. Elimination of various drugs through the kidneys can be severely diminished by hypothyroidism. A classic example would be the elimination of digoxin, which is impaired in patients with hypothyroidism. This could induce severe or even life-threatening cardiac arrhythmias. This is also true for many of the anesthetic agents used for surgery. From the discussion above, it is easy to see that hypothyroidism-induced changes in the renal function and fluid and electrolyte balance can have additive adverse effects on surgical outcomes. Table 3 summarizes the renal, fluid, and electrolyte effects associated with hypothyroidism.

Effects of hypothyroidism on the hemopoietic and coagulation systems

The most common complete blood count abnormality in a hypothyroid patient is that of anemia, occurring in about 25% to 50% of these patients. It is usually a normochromic, normocytic anemia and these patients have normal iron stores, with a hypocellular bone marrow with normal red cell differentiation [34]. Iron deficiency is sometimes seen, especially in premenopausal women who develop menorrhagia because of their hypothyroidism. Also, autoimmune hypothyroidism is occasionally associated with pernicious anemia [35] and the resulting B12 deficiency can induce a macrocytic picture. No significant effect has been documented on any of the white blood cell populations.

There are reports in the literature of patients with a bleeding diathesis associated with hypothyroidism. It is mostly a mild form although severe cases have been described, as in a patient with bleeding from the small intestine that required a total of 54 units of blood. This patient's coagulopathy resolved only after hypothyroidism was diagnosed and treated [36]. As far as the coagulation cascade is concerned, a decrease in plasma factor VIII concentration is the most consistent finding in hypothyroid patients [37], together with a prolonged partial thromboplastin time. Acquired von Willebrand's disease is also seen [38]. Possible etiologies include a decrease in plasma factor VIII coagulant activity and von Willebrand antigen

Table 3
Renal, fluid, and electrolyte changes seen with hypothyroidism

Parameter	Effect
Renal perfusion	Decreased
Hormonal effects	
Antidiuretic hormone	Increased
Atrial natriuretic factor	Decreased
Renin-angiotensin system	Decreased
Serum electrolytes	
Sodium	Decreased
Blood urea nitrogen	Normal to increased
Creatinine	Normal to increased
Creatinine clearance	Decreased
Renal drug clearance	Decreased

activity. In clinical practice, it is commonly a surgical or dental procedure that unmasks the effects of hypothyroidism on the coagulation cascade. Desmopressin has been used for the treatment of this acquired form of von Willebrand's disease, because it stimulates release of factor VIII from the endothelial cells and platelets. Usually, however, only levothyroxine is required to adequately treat these abnormalities.

On the other hand, patients with hypothyroidism have been noted to have a prolonged half life of several other coagulation factors, such as factor II, VII, and X [39]. The clinical significance of these changes is seen in patients requiring warfarin therapy (as for example is the case for patients undergoing orthopedic procedures requiring anticoagulation to avoid the commonly occurring complication of deep venous thrombosis or pulmonary embolism). As a result, it may take longer to adequately anticoagulate these patients. This condition may also necessitate either prolonged heparin therapy until a therapeutic effect of warfarin is seen or larger amounts of warfarin (up to 3 times the dose euthyroid patients need). Conversely, correction of hypothyroidism will generally lead to a reduced warfarin requirement in anticoagulated patients.

Finally, an effect of hypothyroidism on platelet function has been investigated. The acquired von Willebrand's disease noted above is one mechanism that would induce decreased platelet adhesiveness. On the other hand, increased adenosine diphosphate (ADP) and collagen-induced aggregation of platelets [40] may induce altered function with increased adhesiveness. The relative importance of each of these effects remains to be evaluated. As stated earlier, adequate therapy with levothyroxine is required to correct these abnormalities. Table 4 summarizes the hematologic effects of hypothyroidism with emphasis on the perioperative patient.

Effects of surgery on thyroid parameters

Not only does hypothyroidism have a significant effect on different surgical parameters, but the reverse is also true. The stress of surgery has a direct effect on the thyroid axis with alteration in concentrations of TSH and T3. Several clinical and experimental models have been studied, and the effect of cardiac surgery is discussed later. Patients undergoing surgery will manifest the classic euthyroid sick syndrome (ESS) [41,42]. Total T3 is decreased 30 minutes after induction of anesthesia and remains low for at least the first 24 hours postoperatively. Free T3 is also decreased slightly, after an initial increase in the absolute percentage of free hormone on the day of the surgery. Free T4 seems to respond similarly to free T3. Observed alterations in serum total T4 will vary depending on the type of anesthesia, with an increase associated with general anesthesia, whereas a slight decrease in T4 is seen with epidural anesthesia. Serum reverse T3 (rT3) remains unchanged early in surgery, but then its levels usually increase and stay elevated until the fourth or fifth postoperative day. Serum TSH

Table 4
Hematologic effects of hypothyroidism

Hematologic effect	Result
Complete cell count	
Hematocrit	Decreased
Mean corpuscular volume	Normal, may be increased (B-12 deficiency) or decreased (iron deficiency due to menorrhagia)
White blood cell count	Normal
Platelet count	Normal
Bone marrow	
Cellularity	Decreased
Maturation	Normal
Iron stores	Normal (may be low with menorrhagia)
Coagulation	
Factor II	Increased
Factor VII	Increased
Factor VIII	Decreased
Factor X	Increased
APTT	Normal or prolonged
Platelet function	Acquired von Willebrand's disease possible
Response to warfarin	Higher dose frequently required

concentrations remain unchanged with the exception of an increase seen at the time hypothermia is induced. Should the response of TSH to thyrotropin releasing hormone (TRH) be assessed, it will be seen to be somewhat blunted, and cortisol has been implicated as at least one of the causative factors for these changes. Surgery induces an increase in serum cortisol, which may precede the changes seen in the thyroid axis, suggesting a possible causal relationship. This relationship, however, may be over-simplified because the same changes in the thyroid axis were noted in other studies in which the rise of cortisol with surgery was abolished. At the time elderly patients undergoing emergent surgery were evaluated, similar changes were noted [43]. In this study, the more severe the ESS at presentation (as defined by a ratio of T3/reverse T3 < 3), the worse the surgical outcome. The severity of the ESS in these patients also correlated with the severity of hypoalbuminemia and malnutrition. The data from the earlier discussion are consistent with other reviews of the ESS in critically ill patients [44]. Based on this information, it is unlikely that treating such patients with thyroid hormone would be beneficial in the absence of hypothyroidism. Hypothyroidism, however, may coexist with the changes in thyroidal economy seen in the ESS, and the assessment of such patients becomes even more difficult in this setting. In these circumstances the astute clinician must use thoughtful clinical judgment. To help uncover the possibility of an underlying hypothyroid state, a detailed history should be obtained from the patient or the family about prior thyroid diseases, thyroid surgery, radiation therapies (radioactive iodine or neck irradiation), treatment with any "thyroid medicines," or family history of thyroidal illness. A detailed physical examination

is of equal importance. Classic signs of hypothyroidism, such as the dry skin, a slowed deep tendon reflex relaxation phase, bradycardia, hypothermia or the presence of a goiter must be sought. Some may be difficult or impossible to assess, as for example in the patient in the intensive care unit who is intubated and actively sedated. In general, the combination of a low serum free T4 and significantly elevated thyroid stimulating hormone (TSH) are not consistent with ESS and are suggestive of hypothyroidism. If such a picture is present, replacement with T4 is indicated to render the patient euthyroid.

Thyroid hormone therapy in the perioperative "euthyroid sick" syndrome

Under the impression that surgical patients with the low serum T3 and occasional low serum T4 levels typical of the "euthyroid sick syndrome" might benefit from restoration of hormone levels to normal, studies have been conducted to evaluate the role of parenteral thyroid hormone replacement during surgery. Most of the available data comes from animal studies or from patients undergoing cardiac surgery. From animal studies, there is some evidence indicating that thyroid hormone replacement has a positive effect on cardiac muscle postoperatively. Stimulation of isolated cardiac muscle with T3 results in a positive inotropic effect that seems to be dose dependent [45]. In one study in which animals underwent cardiopulmonary bypass, a reduction in creatine phosphate and adenosine triphosphate together with a significant increase in lactate levels was seen [46]. Termination of the bypass by removal of the aortic clamp resulted in reactivation of aerobic metabolism and reversal of the above features. Whereas these studies were not well controlled, the investigators concluded that T3 administration was associated with faster and improved recovery of ischemic myocardial tissue [46]. The results of parallel model studies in humans, however, do not clearly support this finding, and there is some concern regarding reversing what may be a physiologic response to stress. For example, repletion of T3 by exogenous administration could promote an adverse interaction of the thyroid hormone with the increased perioperative levels of catecholamines [27].

Perioperative administration of thyroid hormone to previously euthyroid patients has been examined following cardiovascular surgery, including cardiac transplantation, CABG, and valve replacement surgery [47,48]. The use of intravenous T3 as an inotropic agent has been advocated because it has been associated with a significant improvement in heart rate, mean arterial pressure, central venous pressure and left atrial pressure. As a result T3 has been suggested as an alternative inotropic agent when other hemodynamic support measures have failed. Early data suggested that intravenous T3 administration was potentially beneficial for patients, in whom circulatory failure seemed imminent [48]. These investigators proposed that inotropic support could be reduced or discontinued earlier because of improvement of hemodynamics as early as 1 hour after administration of intravenous T3.

Many early studies, however, suffered from lack of a carefully controlled experimental design and the absence of long-term follow-up data.

Conceivably, an important factor influencing the usefulness of intravenous T3 in the cardiac surgery patient is the degree of cardiac dysfunction [49]. Patients with an ejection fraction (EF) of 40% or more seem more likely to undergo hemodynamic improvement, although there does not seem to be any benefit in earlier discontinuation of inotropic support. On the contrary, for patients with an EF of less than 30%, the opposite seems to be true. The need for inotropic support is less throughout the first 24 hours after surgery but no significant improvement of their various hemodynamic parameters or perioperative mortality has been noted. Surprisingly, one study of patients undergoing CABG with or without T3 supplementation found a decreased rate of atrial fibrillation with T3 replacement, rather than the increase that might have been expected [50].

Although it was rational to presume that cardiovascular status might benefit from T3 administration because of known effects of T3 on cardiac indices, carefully controlled studies indicate no benefit on outcome or the need for standard postoperative care [51,52]. Therefore, we propose that there seems to be no role for T3 supplementation simply to attempt to reverse the known changes seen in the thyroid axis seen in patients undergoing cardiac surgery. Until more convincing data are available, the authors believe that it prudent to consider the potential for adverse effects of T3 in cardiac patients (such as increased myocardial oxygen demand, coronary spasm, arrhythmia and, ultimately cardiac ischemia) before using T3 therapy in such circumstances.

Surgery and the hypothyroid digestive system

The gastrointestinal dysfunction accompanying hypothyroidism may significantly complicate the management of the postoperative patient. Decreased gastrointestinal motility or even ileus is a common complication of surgery, especially after procedures involving the abdominal cavity. Patients with hypothyroidism may suffer from chronic constipation. Atony and hypomotility of the GI tract are well described entities in these patients who may even go on to develop paralytic or ''myxedema ileus.'' Rarely megacolon can develop, which in childhood can mimic Hirschprung's disease. Severe distention of other parts of the GI tract (eg, esophagus, stomach, and duodenum) has also been described. It is entirely possible that the compounded effects of surgery in the presence of hypothyroidism could exacerbate these complications and worsen the surgical outcome with increased morbidity or even mortality.

Several molecular and cellular factors could potentially contribute to the gastrointestinal dysfunction seen in hypothyroidism. Thyroid hormone stimulates the Na-K ATPase activity and the electrogenic sodium absorption in the gut. Also, there is some evidence to suggest that thyroid

hormones are important for the absorption of amino acids and sugars in the intestine [53,54]. The stomach may be another important target for thyroid hormone. For example, hypergastrinemia has been described in cases of hyperthyroidism [55] and the opposite (hypogastrinemia) in cases of hypothyroidism [56]. This condition seems to be independent of the association of autoimmune hypothyroidism (the most common cause of hypothyroidism) and autoimmune gastritis with its resultant decreased gastrin release and achlorhydria. Finally, an enterohepatic circulation of thyroid hormone has been documented, [57] and it is possible that the presence of thyroid hormone in the intestine has direct effects on intestinal function. For example, thyroid hormones could affect the responsiveness of the intestine to secretory hormones such as vasoactive intestinal polypeptide. Whether these interactions have any significance in the clinical setting is not clear but it is possible that the malabsorption and worsening intestinal motility that can be seen in the postoperative period (and especially after intestinal resection) could be exacerbated in the presence of hypothyroidism.

Not uncommonly, surgical patients require prolonged periods of intestinal rest and have no oral intake. Starvation or malnutrition for prolonged periods of time, as can occur in the intensive care unit, is associated with changes of the thyroidal axis consistent with the ESS [44]. There is evidence to suggest that such changes are homeostatically protective and slow down muscle breakdown.

Parenteral thyroid hormone therapy in hypothyroid patients unable to take oral medications

Patients with previously documented hypothyroidism may require an alternative route of administration of their levothyroxine in the perioperative period to maintain euthyroidism. Levothyroxine (T4) and triiodothyronine (T3) are available for intravenous administration. In general, about 70% to 80% of the administered T4 is absorbed in the proximal small intestine (jejunum) [58], and many drugs such as sucralfate [59] or iron may influence absorption. Given the incomplete absorption or oral levothyroxine, the intravenous dose of levothyroxine should be reduced by approximately 20% to 40%. Intravenous levothyroxine therapy will be as effective as oral therapy in improving most if not all of the effects of the hypothyroidism [60]. In contrast to T4, almost 100% of an oral dose of T3 is absorbed, although few indications exist today for its administration, with the possible exception of myxedema coma.

Summary

Hypothyroidism is a common disorder affecting the cardiovascular, respiratory, hematopoietic, and renal organ systems—each of which is particularly germane in the management of the surgical patient. In general, treatment of recognized hypothyroidism is recommended before any

surgical procedure whenever possible and euthyroidism should be documented by measurement of serum TSH as part of the preoperative evaluation. Such a strategy is likely to result in better surgical outcomes with improved morbidity and mortality. One exception to treating first with thyroid hormone is the patient with angina or coronary artery disease requiring bypass grafting, angioplasty or stenting. In this setting, preoperative thyroid hormone therapy could tax the ischemic myocardium. The coronary blood flow should be addressed first, and thyroid hormone therapy initiated afterwards.

The authors have emphasized the need for caution in the interpretation of low serum thyroid hormones in sick or surgical patients because of the importance of distinguishing between hypothyroidism and the "euthyroid sick syndrome." There is no clear evidence at this point to support thyroid hormone replacement in the latter patients, and it may be potentially harmful. Rather, we hold that T3 treatment of various surgical and other patients with nonthyroidal illness should be deferred until proof of its therapeutic efficacy is demonstrated.

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