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THYROID FUNCTION IN THE INTENSIVE CARE UNIT SETTING

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The examination and understanding of thyroid function perturbations in the intensive care unit (ICU) setting is often difficult, because the changes reflect apparent alterations in the ability to measure thyroid hormone parameters and homeostatic modulations in thyroid hormone metabolism accurately. Present concepts suggest that patients in the ICU setting are catabolic and that decreased extrathyroidal conversion of T4 to T3 decreases unnecessary energy expenditure. These alterations in thyroid function in a euthyroid, systemically ill patient are referred to as the euthyroid sick syndrome.[8–10, 18, 49–53] There are selected patients in the ICU who actually have biochemically perturbed thyroid function, either hypothyroidism or hyperthyroidism, in addition to the typical changes of the euthyroid sick syndrome. It is usually difficult to discern these patients from the larger population of euthyroid patients, partly because the usual clinical manifestations of hyper- or hypothyroidism overlap with the signs and symptoms of euthyroid patients who have altered results of thyroid function tests. Further, there is no absolute gold standard clinical or biochemical measurement that can be used to differentiate these two groups of patients. The purposes of the present article are to review the typical thyroid hormone alterations in the euthyroid sick syndrome and to discuss methods of differentiating this syndrome from pathologic thyroid dysfunction that requires specific thyroid therapy. The purpose of assessing thyroid function in a given

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patient is to assess the systemic metabolic action of thyroid hormones at the cellular level. Indeed, serum thyroid hormone measurements, no matter how accurate, may not be proportional to thyroid hormone action at the cellular level.

Sensitive thyrotrophin (third generation) assays that are capable of detecting .01 μU/mL of thyroid stimulating hormone (TSH) have been extremely helpful in this setting and have largely supplanted the need for performing a thyrotrophin releasing hormone (TRH) test.[43, 44] Assuming a normal pituitary gland, a serum TSH measurement in an ambulatory (noncritically ill) patient is the best measure of thyroid hormone action at the cellular level; an elevated TSH concentration shows hypothyroidism and a decreased or undetectable TSH level demonstrates hyperthyroidism. In patients in the ICU, these general principles apply, albeit with several important caveats that are discussed farther on.

ALTERATIONS IN THYROID ECONOMY WITH NONTHYROIDAL ILLNESS

Serum T4 concentration. Although serum total T4 (TT4) concentration is typically normal, nonthyroidal illness may be accompanied by a decline in total T4 concentration. This decrement in serum total T4 may be related to suppression of the hypothalamus or pituitary, decreased T4 related to disordered iodine uptake or hormonogenesis, or a decrease in binding proteins in serum. It seems that the decreased T4 has a multifactoral etiology and it has become apparent in this setting that measurement of the free T4 is much more beneficial than TT4 and, in fact, has largely supplanted it. The best method to measure free T4 in this circumstance is by a direct, nonanalog method. Free T4 metabolic clearance appears accelerated in critically ill patients, but the derived T4 production rate is normal or only slightly decreased.[26, 48, 51]

T4 to T3 conversion. The euthyroid sick syndrome is marked by decreased concentrations of serum T3, suggesting the origin of the synonymous expression low T3 syndrome.[41, 51] Normally, approximately 35% to 40% of the T4 secreted by the thyroid is eventually monodeiodinated and converted to T3, thereby accounting for 80% to 90% of all circulating T3. The remaining 10% to 20% is derived by direct thyroidal T3 secretion. A decrease in serum T3 implies decreased 5'-deiodination and, in view of continuing T4 degradation, further suggests that the T4 is being deiodinated by an alternative pathway. Because T3 is considered the active thyroid hormone, this alternative deiodinative route has been called the inactivating pathway, and it is thought to be mediated by another enzyme, 5-deiodinase, that results in formation of reverse T3 (rT3).

T3. The normal range for serum T3 by chemiluminescence is approximately 80 ng/dL to 180 ng/dL, with most assays having a sensitivity of approximately 10 ng/dL to 15 ng/dL. In the euthyroid sick

syndrome, it is not unusual for T3 to be undetectable. It is reduced T3 production rather than augmented T3 degradation and disposal that is responsible for the observed low values for serum T3. Although theoretically the decrease in serum T3 may be desirable to the organism to conserve energy, the critical question of whether prolonged T3 deficiency may be deleterious to survival remains to be answered.[41, 51, 53]

The determination of free T3 in serum (which ranges from 0.2 ng/dL to 0.4 ng/dL) would, theoretically, obviate the potential difficulty interpreting bound iodothyronines and should be a better measure of thyroid hormone pathophysiology than the total T3. Although the free T3 measurement is rapidly becoming clinically applicable, for technical reasons it has not yet become routinely available with a clinically relevant turn around time. Whether or not the metabolic activity of the thyroid hormones depends entirely on the conversion of T4 to T3 with T4 relegated to the role of only a prohormone is still controversial. The evidence for a significant metabolic role for T4 remains to be determined if a decreased serum T3 signifies less thyroid hormone action at the cellular level. In certain patients, the presence of normal serum T4 and TSH concentrations, in conjunction with decreased T3, suggests that T4 may possess important biologic activity itself.

rT3. Elevated levels of rT3 have been described in a wide variety of systemic illnesses, such as infectious diseases, cirrhosis, starvation, myocardial infarction, and a host of other acute, nonspecific, nonthyroidal disorders.[14, 51, 52] Caloric deprivation is associated with low T3/high rT3. The organism may be attempting to conserve energy by decreasing T3 production and its basal metabolic rate, because administration of T3 to starving subjects results in greater muscle catabolism with increased nitrogen and 3-methylhistidine excretion.[11, 49] Kinetic analysis in normal individuals has suggested mean values for metabolic clearance rates (MCR) ranging from 77 to 112 liters/day/70 kg and for production/disposal rates of 34 to 52 μg/day/70 kg. The rT3 clearance decreases during fasting, presumably because of the same decreased 5′-deiodinase activity responsible for decreased T3 generation from T4.[21]

Although theoretically reverse T3 should be elevated in the euthyroid sick syndrome and decreased in hypothyroid subjects, Burmeister[12] has shown that serum reverse T3 could not be accurately used to determine whether patients have hypothyroidism or euthyroid sick syndrome.

Thyroid Hormone Binding and Transport

T3 resin uptake. The T3 resin uptake test has traditionally been used as an indirect measure of thyroid hormone binding. This test cannot assess thyroid hormone levels or function. Although this test was commonly used in clinical circumstances, its routine measurement has now virtually been supplanted by an improved ability to measure thyroid hormones directly. The T3 resin uptake may be used as a multipli-

cand with the total T4 to yield a free thyroxine index (FTI), which is an estimate of the actual free T4 concentration. This estimate may be valid in patients with minor illness; however, because of limitations inherent in the method, this correlation does not apply to patients with severe nonthyroidal illness. It is much preferable to measure free T4 and free T3 in systemically ill patients rather than using a calculated index, especially when the index is based on the T3 resin uptake test.

Free T4. *Direct measurement of free T4 is now routinely available.* Chopra[20] used a direct equilibrium dialysis radioimmunoassay to demonstrate that free T4 was normal in most patients with euthyroid sick syndrome and free T3 was normal in approximately 83% of patients with the low T3 syndrome. [13]

Chopra and co-workers[15] have suggested the presence of a circulating inhibitor of thyroid binding in patients with nonthyroidal illness. Observed increases in the dialyzable fraction after addition of serum from patients with nonthyroidal illness suggests the presence of a substance that inhibits thyroid hormone binding by normal serum proteins. Free fatty acids have many similar characteristics of this inhibitor. Other workers[34] have failed to detect the presence of endogenous binding protein inhibitors in sera of sick patients.

Recent studies have suggested that cytokines may be responsible, at least in part, for the iodothyronine alterations in the euthyroid sick syndrome. Davies and co-workers[17] showed a relationship between interleukin-6 (IL-6) concentrations and the thyroid changes seen in euthyroid sick syndrome. Torpy and colleagues[46] showed that IL-6 administration in healthy humans could lead to thyroid function test results that mimicked the euthyroid sick syndrome. Nagaya and colleagues[36] suggested that nuclear factor (NF) kappa B activation by TNF alpha may also contribute to the euthyroid sick syndrome.

TSH. Serum TSH concentrations are typically normal in patients with nonthyroidal illness, although occasionally the levels may be slightly decreased or increased. Rarely are serum TSH levels undetectable in euthyroid patients with nonthyroidal illness alone. Serum TSH levels may be decreased in a variety of physiologic or pathologic states, including those induced by corticosteroid or dopamine administration, somatostatin administration, and fever or stress.[35] Levels of TSH become elevated with decreases in serum thyroid hormone because of removal of physiologic feedback inhibition, and elevated TSH levels are regularly seen in primary hypothyroidism. In patients with nonthyroidal illness and decreased levels of serum T4 and T3 the determination of serum TSH should help indicate if the patient has biochemical hypothyroidism. This interpretation, of course, depends on the hypothalamic-pituitary axis being intact, and it frequently is not easily possible to determine if pituitary or hypothalamic disease is present. Exogenous steroids, diphenylhydantoin, and dopamine infusions may decrease endogenous TSH secretion, obscuring the fact that the patient has primary hypothyroidism and would have an elevated TSH level in the absence of these agents. To complicate matters further, serum TSH in patients with non-

thyroidal illness may have a discordant ratio of biologic to immunologic potency such that the level that is measured may overestimate the biologic potency. The hypothalamic-pituitary axis may not respond normally to changes in serum iodothyronine levels. Maturlo and colleagues[32] measured TSH before and after inducing further decrements in serum T4 and T3 by administration of stable iodine. Basal TSH levels rose in only 11 of 23 patients, leading these authors to suggest that the finding of a normal serum TSH concentration in a patient with systemic illness may not be a reliable index of euthyroidism. Bacci and coworkers[2] recently speculated that the lack of the expected rise in TSH as a result of low circulating T3 and T4 in critically ill patients may be a result of stress, hypothermia, or both. During the recovery period of severe illness, the investigators observed that TSH increased even when serum T3 was still below normal levels and that TSH levels were relatively higher in hypothermic than nonhypothermic ill individuals. It is well known that TSH may increase, even rising above the normal range, in patients in the process of recovering from nonthyroidal illness. Despite the inherent problems in interpreting serum TSH concentrations in patients with euthyroid sick syndrome, it remains the best single test to help discern euthyroid individuals from those with hyper- or hypothyroidism. This test result must be interpreted in the context of clinical history, examination, and administered pharmacologic medications.

Development of highly sensitive immunoradiometric and chemiluminescent assays for TSH has represented arguably the most significant advance in the diagnosis and management of thyroid disease in the past decade. Euthyroidism is inferred in sick patients on the basis of normal rather than elevated TSH values, but results of measurements with the newer TSH assays indicate that normal values cannot always be anticipated. Although TSH levels in most hospitalized patients are normal, about 20% to 25% of hospitalized patients will have abnormal TSH levels. Even elevations of TSH above 20 mU/L did not always signify hypothyroidism, for virtually half of the patients with such values were euthyroid, their high TSH levels representing recovery from nonthyroid illness.[21, 43, 51]

MISCELLANEOUS FACTORS ASSOCIATED WITH ALTERED THYROID ECONOMY

Age

The effects of age on thyroidal economy have been reviewed.[2, 6] The normal aging process appears to be associated with a decrease in the MCR and turnover of T4. Given that serum total T4 is unchanged or decreased, this occurrence implies that T4 secretory rate from the thyroid must be similarly decreased.

Measurement of serum TSH in a patient without hypothalamic-pituitary disease is thought to be the most accurate indicator of T4/T3

action at the cellular level, assuming the patient is not taking medications known to affect this axis. In certain circumstances, such as in the aged individual, however, a normal TSH level may not always be a valid index of euthyroidism because regulation of the hypothalamic-pituitary axis may be impaired; only 50% of aged patients will augment their TSH response to TRH after iodine-induced decrements in their serum T4 and T3 levels. Although some workers have found slight but significant decreases in serum TSH concentrations in a healthy geriatric population in comparison with a younger control group, several other reports indicate that basal TSH levels are probably stable throughout life.[39] In sum, serum TSH is considered the single most useful biochemical test to identify patients with primary hypothyroidism or even hyperthyroidism.

Effects of Miscellaneous Environmental Factors and Stress

Drugs

The following section highlights effects of those drugs that are used with frequency in patients with systemic illness and might be likely therefore to contribute to confusion in the assessment of such patients, particularly those in the hospital intensive care setting.

Dopamine. Dopamine infusion will lower both basal TSH level and blunt the TSH response to TRH,[28] suggesting a physiologic role for endogenous brain dopamine in the control of TSH secretion. The prolonged infusion of dopamine may lead to a secondary hypothyroidism; such infusions are rarely of sufficient duration that the patient requires thyroid hormone replacement, given the 5 to 7 day half-life of T4. Dopamine agonists can decrease the elevated TSH levels of patients with primary hypothyroidism, in some cases obviating the elevated TSH level observed in patients with primary hypothyroidism. An infusion of dopamine agonists typically lowers serum TSH rapidly and its effects are dissipated in a short time period. Dopamine antagonists can elevate both basal and TRH-stimulated levels of TSH, although these alterations are slight and probably would not lead to any diagnostic confusion.

Glucocorticoids. Glucocorticoids may be administered in pharmacologic doses to patients with a wide variety of allergic or autoimmune disorders with resultant blood levels that may profoundly influence thyroid function at several levels. Suppression of both basal and TRH-stimulated TSH release is likely to be seen in such patients, as well as in those with elevated endogenous cortisol levels caused by either stress or Cushing's disease.[19, 20]

Corticosteroids will decrease thyroid hormone binding to its proteins, but the measured free T4 and T3 levels should be normal. Glucocorticoids inhibit T4 to T3 conversion, which results in a lowering of serum T3 concentration. In a patient with systemic illness, this effect

would further compound the low T3 and high rT3 likely to be already present. The steroid effect may be seen within 24 to 36 hours, and the magnitude of change will depend on the specific drug, dose, and route of administration.

Iodine. A brief consideration of the effects of iodine on thyroid economy is also warranted because hospitalized patients may undergo a variety of radiographic procedures with contrast dyes yielding extraordinary iodine loads to the patient. Iodine acutely inhibits the secretion of thyroid hormone,[54] an effect that is exploited in the treatment of hyperthyroidism but that can produce undesired hypothyroidism in certain vulnerable individuals. Thus, declining T4 and T3 values accompanied by rising serum TSH in a patient with prior history of thyroid disease warrants a search for history of iodine excess. In the ICU setting, the hypothyroid patient may present with unexplained hypothermia or failure to manifest fever with infection, rising serum creatine phosphokinase (CPK) enzymes, or unexplained carbon dioxide (CO_2) retention. In patients with underlying autonomous thyroid function (e.g., euthyroid Graves' disease, solitary hot nodules, multinodular goiter), iodine surfeit may present with thyrotoxicosis.[47] Thyrotoxicosis complicating serious systemic illness might be best excluded by obtaining serum T3 and free T3 concentrations that would be high in hyperthyroidism and low in systemic illness.

Iodinated contrast agents. In addition to the previously mentioned potential problem caused by their iodine content, several contrast agents that are used with moderate frequency in hospitalized patients have other specific effects on thyroid economy. Most commonly today, iodinated agents are used for angiographic studies, perhaps of coronary, cerebral, abdominal, or peripheral arteries. These agents act mainly to decrease hepatic conversion of T4 to T3,[55] although they also probably decrease hepatic uptake of T4 and possibly binding of T3 to nuclear receptors. The decrease in deiodination affects the outer iodine ring, with less T3 neogenesis and less rT3 degradation, resulting in a low T3 (high rT3) syndrome. These dye-induced abnormalities generally persist for no more than 2 to 4 weeks after administration of the drug. The most common clinical effect of radiopaque agents is decreased T4 to T3 conversion caused by the chemical compound itself and diminished thyroidal secretion secondary to an iodine effect. Only rarely do these agents cause hyperthyroidism, considered an iodine effect. Unfortunately, the majority of the published studies on this topic analyzed cholecystographic agents that are rarely used at present, and it is not precisely known if the effects of various angiographic agents are comparable in extent and duration.

Amiodarone. Amiodarone is an antiarrhythmic agent that is finding increasing applications in the United States. In customarily used dosages, the drug will cause a low T3 syndrome similar to that seen with the iodine-containing contrast agents (amiodarone is 37% iodine), marked by a decreased T3, increased rT3, and variable to slight increases in serum T4.[33] Using larger therapeutic doses, Melmed and co-workers[33]

recently confirmed these findings and further showed that free T4 and total T4 were elevated and that both basal TSH and TRH-stimulated TSH release were found to be augmented rather than suppressed, as might have been expected in patients with a high free T4. Consequently, it is likely that the drug inhibits T4 to T3 conversion and T3 binding in the pituitary, as has been described for iopanoate. The bradycardia that almost invariably accompanies high-dose amiodarone therapy should not be taken as a sign of hypothyroidism, and general awareness of the effects of these agents on the pituitary-thyroid axis should obviate an erroneous diagnosis. Amiodarone may cause hypothyroidism, especially in countries where iodine intake is sufficient. Alternatively, it may cause hyperthyroidism (especially in countries where iodine intake is deficient) that may be a result of excess iodine or a direct toxic effect on the thyroid gland. Before administering amiodarone, baseline thyroid function tests should be performed, and periodic measurements should be obtained while the patient is taking this medication, and for several months thereafter.

In brief, in the proper clinical circumstances, an elevated TSH level in conjunction with a decreased serum free T4 level suggests primary hypothyroidism and, in contrast, an elevated serum level free T4 level, normal or increased T3 and free T3 and undetectable TSH suggests hyperthyroidism.

Diphenylhydantoin. Diphenylhydantoin (Dilantin) or phenytoin is commonly used for seizure disorders. This drug results in decreases in serum T4 and rT3 and occasional but not consistent decreases in T3 and free T3,[42] but basal serum TSH and TSH responses to TRH are generally normal. Free thyroxine index (TFI) is usually significantly reduced but free T4 by dialysis may be normal. Although conversion of T4 to T3 and clearance of T4 from blood into tissues is enhanced (accounting for the low free T4 and total T4), these patients should be viewed as euthyroid.

SPECIFIC DISORDERS AND CONDITIONS

Starvation and Fasting

The reader is referred to the opening sections of this article for general comments dealing with several of the factors influencing alterations in serum iodothyronine levels, hormone turnover, and TSH/TRH responses during starvation; recent reviews provide additional information.[45] It may be difficult to discriminate between the effects of absolute or relative starvation and those of a given specific illness in seriously ill patients because malnutrition is a regular concomitant condition of so many acute and chronic disorders. As the now well described reduction in serum T3 in the starving organism is thought to represent an attempt to conserve energy and maintain homeostasis by reduction of metabolic expenditure, experimental attempts to restore serum T3 to the normal range during starvation have resulted in evidence of increased muscle catabolism[11] that is presumed to be detrimen-

tal. The clinician should bear in mind that the starvation-associated alterations in thyroidal economy may not be abnormal at all but rather may represent values that only significantly differ from those seen in the fed state.

General considerations

Serum iodothyronines. Early studies have indicated that total fasting led to a decrease in thyroidal iodine uptake.[45] In clinical studies, most workers have found either little change in serum total T4 or free T4 concentrations or slight decrements; these levels tend to return toward normal during continued starvation. Thyroidal T4 production and secretion may be reduced during fasting.[51, 53]

The percentage of free T4 or unbound T4 and/or the free T4 concentration may increase during fasting, although free T4 concentrations also may be normal or unchanged.[51, 53] Increases in free T4 may be the result of decreased binding of T4 caused by an inhibitory effect of plasma free fatty acids that are known to increase during starvation.

Fasting results in dramatic decreases in serum total T3 within 24 to 48 hours.[51, 53] The absolute free T3 concentration is similarly reduced. The 5-deiodination of an iodine atom from the nonphenolic ring of T4, resulting in formation of rT3, is increased during starvation, and the percent conversion of T4 to rT3 has been observed to increase from 41.8% to 61.1%.[45] Indeed, increases in serum rT3 during fasting or starvation have been universally seen, probably related at least in part to decreased clearance.

Diet-induced alterations is serum T3 were shown by Glass and coworkers[23] to depend on the composition of the diet rather than a reduced intake of either total calories or protein. Several experimental studies had suggested a primary role for glucose, and this role was confirmed by subsequent clinical studies indicating that only 50 g (200 Cal) carbohydrate (glucose) was adequate to reverse fasting-induced alterations in serum T3 and rT3; a similar response was seen if the calories were furnished as fructose.[10]

Refeeding fat has little effect in restoring iodothyronine levels to normal and the replacement of dietary carbohydrate with fat on an equimolar basis still results in a marked fall in circulating serum T3 and a rise in rT3,[16] so carbohydrate appears to be the key ingredient of the diet. Fat may play a separate role in altering thyroid metabolism because decreases in T3 and increases in rT3 may be seen in the presence of an adequate carbohydrate and caloric intake when fat is simultaneously provided in high concentration. O'Brien and co-workers [38] found that feeding protein (400 Cal) did not prevent a fall in serum T3, a rise in rT3, or blunting of TSH response to TRH. The blunted TRH seen with fasting tends to occur with any hypocaloric diet associated with altered T3 levels.[38]

TSH and TRH response. Basal TSH levels are either unchanged or decreased. TSH levels may remain lower than control values even after

an initial (5-day) refeeding period sufficient to restore serum T3 and rT3 levels toward normal. A significantly blunted response is typically seen during fasting. Gardner and co-workers[22] demonstrated that administration of T3 during a fast will further suppress TSH and TRH responses, whereas iodine administration may augment responses appropriately just as is seen in fed individuals, suggesting that feedback is intact but that the pituitary-thyroid setpoint is reset during starvation.

Infection

Shortly after the onset of clinical infection in humans, there occurs a fall in serum T4 and T3 levels, reflecting decreased TSH stimulation of the thyroid, decreased thyroidal secretion, accelerated T4 disappearance, and the effect of inhibition of hormone binding to transport proteins. Therapy of the infection and recovery is associated with resumption of TSH release and thyroidal secretion and a progressive rise in serum T4 and T3 levels. The depression in serum T3 also reflects decreased T4 to T3 conversion. Increases in serum rT3 also have been noted in some infections in which it was measured, presumably on the basis of a decreased clearance.

The series of patients with sepsis reported by Richmand and co-workers[40] demonstrated the typical findings of decreased total T4 and T3, increased free T4 and rT3, and normal TSH seen in other infections. These workers administered different types of nutritional support to their patients to assess the relative roles of caloric deprivation and infection per se in the genesis of the alterations in thyroid function tests. They concluded that caloric deprivation played at least as major a role as the underlying illness in the pathogenesis of the observed changes. Minor differences in results have been seen in other types of infections.

Infection acts to suppress TSH. It remains difficult to determine whether the enhanced endogenous cortisol production accompanying illness or stress and the relative caloric deprivation of this catabolic state might be responsible in toto or in part for the suppression of TRH or TSH release. The normal TSH response and augmented prolactin (PRL) response to TRH seen in subjects with acute malarial infection was interpreted to signify a hypothalamic defect but an intact pituitary reserve.[52]

Malignancy

Although early reports suggested a higher prevalence of raised serum TSH in patients with carcinoma of the breast, this abnormality was found to be less frequent in more carefully controlled studies.[1] Adami and co-workers[1] compared 179 patients with 179 matched controls and did find a higher mean TSH, T3 resin uptake, and rT3, a normal T4, and a decreased serum T3 in the patients with breast cancer but attributed the changes to the effects of concomitant nonthyroidal

illness. A controlled study by Macfarlane and colleagues[45] found only four patients with abnormal results of thyroid function tests among 162 patients with carcinoma of the breast, but they found comparable abnormalities in 5 of 60 patients with benign breast disease and in 6 of 72 control subjects as well. Of the four patients with breast cancer, one had coexistent thyrotoxicosis and three had elevated TSH levels with normal T4 and T3. These studies lead the authors to conclude that malignancy, when associated with systemic illness, may exhibit the nonthyroidal illness but, to date, there are few data indicating that specific malignancies act discordantly on T3, T4, and TSH levels.

Acquired Immunodeficiency Syndrome (AIDS). The usual peripheral thyroid hormone alterations noted in general for the euthyroid sick syndrome apply to AIDS, although further comment is indicated. Patients with AIDS may present with a multiplicity of altered results of thyroid function tests that vary with the progression and severity of the illness.[24, 25, 30] All but the most severely ill patients may maintain normal levels of serum T4 and T3 with a falling serum T3 and a rising thyroxine binding globulin (TBG) level correlating with falling CD4 counts and high mortality. It has been speculated that the normal T3 levels could be counterproductive and serve to worsen the progressive cachexia of patients with AIDS, but this hypothesis has been disputed. [24, 25, 30] Levels of rT3 tend to remain normal or decrease slightly (rather than increase as in other infections), and basal serum TSH and TRH responses also tend to remain normal.

Thyroid Hormone Treatment during Nonthyroidal Illness. Support for thyroid hormone treatment has come from the experimental and clinical studies of Novitzky and co-workers who used a variety of models related to organ transplantation such as brain dead organ donors.[37] T3 may have beneficial inotropic effects on myocardium.

Concerns over the administration of T3 relate to studies indicating negative effects on protein and fat metabolism, an adverse effect on the myocardium by the synergism between T3 and circulating high levels of catecholamines present in systemic illness, and the risks attendant with T3-induced increases in oxygen demand on the coronary circulation with vascular spasm and ischemia leading to arrhythmias and death. In experimental models, chronic T3 administration sensitizes the heart to β-adrenergic stimulation, leading to an exaggerated chronotropic (rate) response and to a paradoxically reduced exercise tolerance. Although the latter may be related to a peripheral rather than a cardiac mechanism, more prolonged thyroid hormone excess might depress ventricular function and exercise capacity even further.

The practical question is whether or not thyroid hormone administration will influence outcome or prognosis of systemic illness. In one experimental study of pneumonitis, rats treated with thyroid hormone died at a faster rate than controls.[29] The available randomized and controlled clinical trials of thyroid hormone administration to critically ill patients have not indicated any therapeutic benefit of T4 or T3.[3,7] An argument can be made that T3 and not T4 therapy would be more

rational in view of the reduced ability of the sick patient to monodeiodinate T4 to T3.

There are studies that used T3 in patients who have undergone coronary artery surgery. In a prospective, randomized clinical trial, Bennett-Guerrero and co-workers[4] investigated 211 patients undergoing coronary artery bypass surgery who were randomized to receive either an intravenous infusion of T3 (0.8 μg/kg) followed by 0.12 μg/kg/h for 6 hours, dopamine (5 μg/kg/m^2) or placebo. Serum T3 levels decreased in the dopamine and placebo groups but did not decrease in the T3 treatment group. There were no significant differences in hemodynamic variables or inotropic drug requirements in either of the groups. Klemperer and co-workers[27] performed a similar prospective, randomized study in coronary artery bypass patients in which one group received T3 (0.8 μg/kg) followed by 0.113 μg/kg/h infusion for 6 hours while the control group received placebo. Postoperative cardiac index was higher in the T3 treated group (2.97 versus 2.67 L/min/m^2) and systemic vascular resistance was lower (1073 versus 1235 dyn-sec-cm^{-2}). There were no differences in the incidence of cardiac arrhythmias, mortality, or requirement for medications. In summary, it appears that T3 administration in these two studies was not associated with significant improvement such that its routine use can be recommended. Bettendorf and colleagues[5] found that treatment of children with T3 after cardiopulmonary bypass surgery improved cardiac function in selected patients and decreased the necessity for postoperative intensive care.

SUMMARY

In sum, there is no convincing evidence yet published supporting the utility of T4 or T3 administration in patients with nonthyroidal illness. The authors recognize that evidence accrued in one disease state may not be applicable to others and that, although these studies are difficult to perform, further large scale prospective studies need to be performed. The issue of T3 treatment will not be resolved satisfactorily until more definitive data are available. Until that time, there may be rare circumstances when a clinician may think it best to treat an individual patient with T4 or T3. For the majority of patients, however, there will be little indication for the administration of thyroid hormones until the potential benefits can be shown to outweigh the risks.

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