Thyroid Emergencies: Myxedema Coma and Thyroid Storm

Department of Internal Medicine Grand Rounds

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James E. Griffin, M.D. has no financial interests or other relationships with commercial concerns related directly or indirectly with this program. Dr. Griffin will be discussing "off-label" uses in his presentation.

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My last grand rounds dealt with the mild (subclinical) forms or hypothyroidism and hyperthyroidism. For these rounds the more extreme end of the spectrum will be considered. These subjects were last reviewed in this forum by Dr. Jean D. Wilson ("Fatal Myxedema" on 12/2/65) and Dr. Daniel W. Foster ("Thyroid Storm" on 4/13/78). One might first wonder how I could presume to cover both subjects in one talk. One reason is that there is not a wealth of new science or clinical insight to discuss. The other is that although myxedema coma and thyroid storm are at the opposite ends of the spectrum of thyroid disease, they share several principles in common. Both present as an acute decompensation of a chronic deficiency/excess state. This decompensation is hallmarked by a precipitating event. And therapy is targeted at: 1) treating the decompensating event, 2) restoring circulating thyroid hormone levels to normal, and 3) supporting respiratory, circulatory, cardiac, and temperature regulation.

Myxedema Coma

Myxedema coma is the term commonly used to describe a life-threatening clinical state associated with longstanding untreated hypothyroidism. Most patients do not have obvious skin changes of myxedema or frank coma. The key features include altered mental status, defective thermoregulation, and a precipitating event or illness.

Physiologic Adaptations to Hypothyroidism

With worsening hypothyroidism oxygen consumption and body heat generation progressively decline. The compensation the body makes for these changes is peripheral vasoconstriction to restrict blood flow to the skin and redirect it to the core to maintain a normal body temperature. This adaptation is manifested clinically by cool pale skin. With more advanced hypothyroidism, the peripheral vasocontriction may lead to mild to moderate diastolic hypertension. Chronic vasoconstriction in severe and prolonged hypothyroidism can lead to as much as a 20% or 1 L decrease in the total blood volume (1).

Thyroid hormone regulates the number of β-adrenergic receptors (2). Although the serum catecholamine levels are usually normal in hypothyroidism, the response to catecholamines is blunted generation of cyclic AMP and reduced effects depending on the organ system studied (3). The decreased β-adrenergic response includes a decreased thermogenic response to epinephrine, which further impairs maintenance of core temperature in a hypothyroid patient challenged by heat loss.

Streeten and colleagues evaluated blood pressure in 40 thyrotoxic patients following thyroid ablation with radioiodine (4). With the development of hypothyroidism 16 patients (40%) had elevations of diastolic blood pressure greater than 90mm Hg. Restoration of euthyroidism with thyroxine adminstration reduced systolic and diastolic blood pressure in these patients, with a fall in diastolic pressure below 90mm Hg in nine of the sixteen. In this same report the authors assessed the prevalence of hypothyroidism in 688 consecutive patients referred for evaluation and therapy of hypertension.

Hypothyroidism was found in 25 (3.6%) of the patients. Thyroid hormone replacement resulted in lowering of the diastolic blood pressure to levels below 90mm Hg in 32% of the patients after withdrawal of all antihypertensive drug therapy when euthyroidism had been restored.

Problems in the Elderly

Oxygen consumption and heat generation decline with age independently of thyroid status. Some of the reduction can be attributed to the 13 to 23% reduction in basal metabolic rate (5,6). This age-related decline in oxygen consumption, when combined with that induced by hyypothyroidism, creates a metabolic problem which may not be easily compensated for. Thus elderly hypothyroid subjects may be at greater risk for decompensation. Dr. Nicoloff has even suggested that finding a "normal" blood pressure in an elderly hypothyroid patient with peripheral vasoconstriction may be an early sign of impending decompensation (7).

Hypothyroidism and the Cardiovascular System

Thyroid hormone has both direct and indirect effects on myocardial function. Studies have shown that thyroid hormone stimulates the level of α-myosin heavy chain in the myocardium of small mammals (8). This isoform of cardiac myosin is associated with a higher level of ATPase activity than the β-isoform. Thus, in smaller mammals, thyroid hormone is a major determinant of contractile velocity. However, in humans and nonhuman primates, β-myosin is the predominant isoform expressed in the adult heart, and it is not altered substantially by either thyroid hormone deficiency or excess (9). Cardiac sarcoplasmic reticulum calcium-activated ATPase (SERCA) and Na/K-ATPase are thought to be directly stimulated by thyroid hormone. In studies of isolated papillary muscle from hypothyroid cats, the velocity of shortening and rate of tension development were markedly slowed compared with muscles from euthyroid animals (10). The isometric tension achieved was not significantly different in muscle from the hypothyroid and euthyroid animals.

Studies in severely hypothyroid human subjects using echocardiography demonstrate a reversible change in myocardial thickness and function (11). Twenty severely hypothyroid subjects (mean age 62) were studied before and six months after thyroxine replacement. Before treatment the interventricular septum and right ventricular wall thickness were increased, and both decreased following thyroxine replacement. Echocardiographic parameters of regional myocardial function (systolic septal thickening) and global ventricular function (fractional shortening of the left ventricle) were decreased before therapy and significantly increased after thyroxine.

The effect of hypothyroidism on left ventricular function at rest and during exercise was studied in nine patients with short term hypothyroidism during preparation for monitoring their previous thyroid cancers by total body scans (12). When the patients were hypothyroid, cardiac output, stroke volume, and end diastolic volume at rest were all lower and peripheral resistance was higher than when they were euthyroid. However,

pulmonary capillary wedge pressure, right atrial pressure, heart rate, left ventricular ejection fraction, and the systolic pressure: volume relation of the left ventricle, which was used as an estimate of contractile state, were not significantly different when the patients were hypothroid or euthyroid. During exercise, heart rate, cardiac output, end diastolic volume, and stroke volume were higher when the patients were euthyroid than when they were hypothyroid. Again PCWP, EF, and the estimate of contractile state were similar in both thyroid states. The authors suggested that the alterations in cardiac performance seen in short term hypothyroidism are primarily related to changes in loading conditions and exercise heart rate. They did not feel that acute hypothyroidism has a major effect on contractile properties of the myocardium.

Many of the reversible changes in myocardial function in severe hypothyroidism may be secondary to changes in the peripheral circulation induced by thyroid hormone deficiency. The preservation of normal arteriovenous oxygen extraction in severely hypothyroid patients with a 35% decrease in cardiac index suggests that the decrease in cardiac output is appropriate for the decrease in total body oxygen consumption (13). These authors evaluated the ratio of cardiac output to oxygen consumption in 12 myxedematous patients and found that it was not significantly different from normal subjects either at rest or during exercise (Figure 1) (13). The cardiac output at rest in the patients was directly related to the level of oxygen consumption. Thus the decrease in cardiac output appears to be appropriate to the decreased metabolic demand.

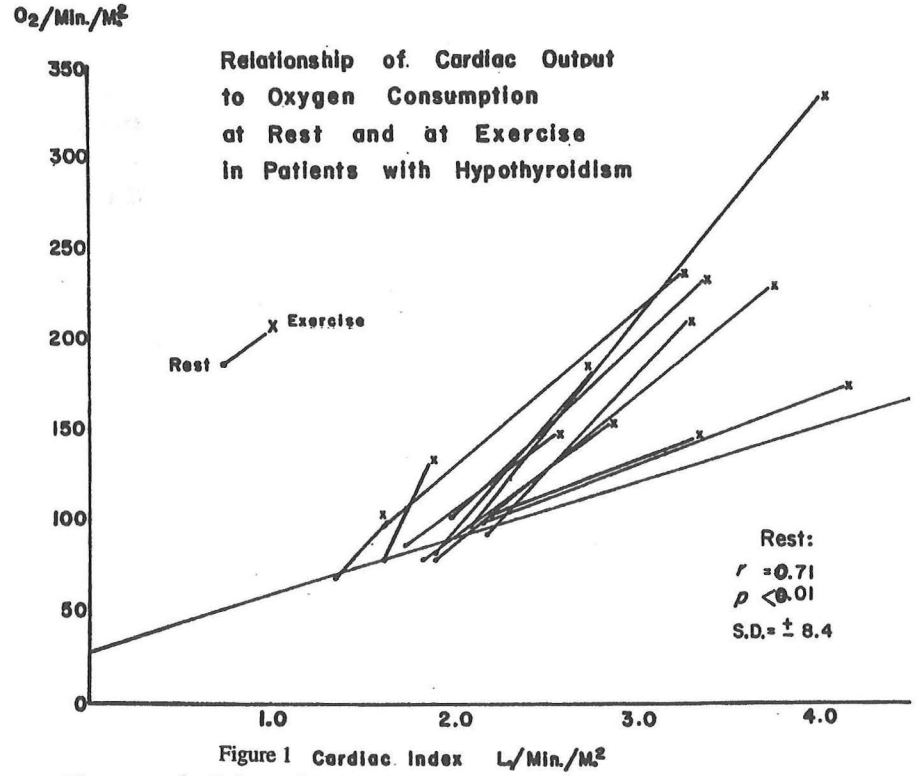


Figure 1 Cardiac Index L/Min./M2

Respiratory Changes in Myxedema

Myxedematous patients have disordered ventilatory drive. Both hypoxic and hypercapnic ventilatory drive is depressed (14). Ten patients with clinically stable myxedema (mean

after thyroxine replacement. They were compared with a group of seven subjects with postsurgical hypothyroidism off their medication for three weeks in preparation for a total body scan to monitor their prior thyroid cancers. Both myxedema and brief hypothyroidism produced depression in hypoxic ventilatory drive that is responsive to replacement therapy (Figure 2 and 3) (14). Hypercapnic ventilatory drive was significantly depressed in the myxedematous patients but not the hypothyroid subjects. Thyroxine replacement resulted in an increase in hypercapnic drive that did not reach statistical significance.

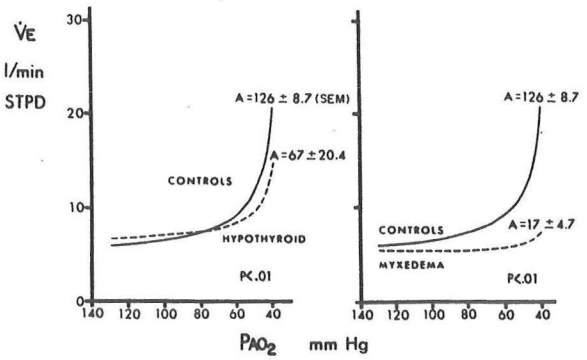


Figure 2 . Ventilatory Responses to Hypoxia Shown as Relation between Alveolar Oxygen Tension (P_{AO2}) and Minute Ventilation ($\dot{V}_E$), Standard Temperature Pressure Dry (STPD).

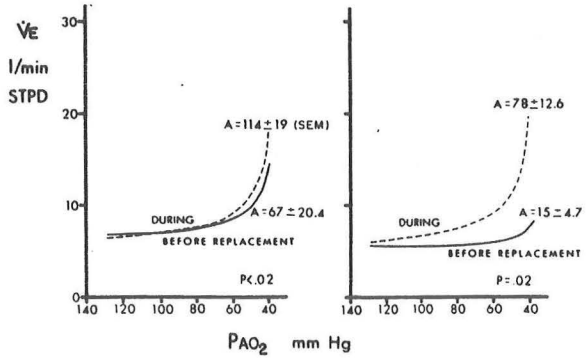


Figure 3 . Effect of Thyroid Hormone Replacement on Hypoxic Ventilatory Drive in the Groups with Hypothyroidism (Left) and Myxedema (Right).

Another group studied the predictors of an abnormal ventilatory response in 35 ambulatory hypothyroid patients (mean age 50) (15). Thirty-nine per cent of the subjects had either abnormal hypoxic or hypercapnic ventilatory drive, and female gender or a serum TSH greater than 90 μU/ml were predictors of an abnormal ventilatory response.

Respiratory muscle weakness may also contribute to ventilatory abnormalities in hypothyroidism (16,17). Four patients with severe hypothyroidism were found to have decreased diaphragmatic strength as evidenced by a reduced maximal transdiaphragmatic pressure. Diaphragmatic strength improved in all patients following thyroxine replacement. In one patient in whom it was tested, phrenic nerve conduction times were prolonged bilaterally (16). The conduction time normalized at three months following thyroxine replacement. Repiratory muscle weakness may contribute to symptoms of weakness, breathlessness, and perhaps hypoventilation in severe hypothyroidism.

Other Metabolic Changes

Although a variety of forms of anemia may be seen in hypothyroidism (18), detailed studies of 56 patients did not disclose abnormalities of serum concentrations of vitamin B_{12}, folate, or iron in the 13 who had a low hemoglobin (19). Most compensated hypothyroid patients have a mild normocytic anemia (hematocrit 30-35%) that is thought to be due to the decreased effects of thyroid hormone on cellular replication in the bone marrow and erythropoietin production (18). This anemia resolves with thyroid hormone therapy. If a more severe anemia is present, other etiologies should be considered.

A decrease in overall metabolic rate accompanying hypothyroidism may result in other manifestations. Hypothyroid patients are said to be prone to hypoglycemia. A decrease in clearance of insulin and decreased gluconeogenesis may be the explanation (20). Impaired responses to counter regulatory hormones may impair recovery from hypoglycemia (7). Decreased clearance of most drugs can predispose to adverse effects from commonly used drugs such as digoxin, diuretics, tranquilizers, and narcotics. Reduced clearance of muscle enzymes (in addition to increased leak) may cloud their use in diagnosis of myocardial injury (21).

Severely hypothyroid patients are often hyponatremic. This has often been attributed in the past to the syndrome of inappropriate antidiuretic hormone secretion. More recent studies with sensitive assays for vasopressin (AVP) do not support inappropriate levels (22). In eight patients with longstanding compensated untreated hypothyroidism, mean serum sodium and plasma osmolality were lower than normal. Mean AVP levels were 0.5±0.1 pmol/L versus 2.5±0.5 pmol/L in normal subjects ($p< 0.01$), and the rise in AVP in response to hypertonic saline was normal or subnormal (Figure 4) (22). Altered renal hemodynamics due to decreased blood volume or cardiac output is the likely mechanism for the impaired water excretion.

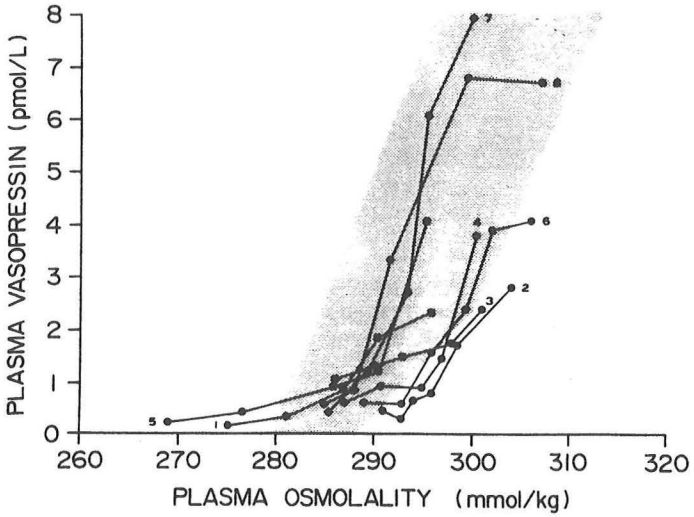


Figure 4. The relationship of plasma AVP to plasma osmolality during hypertonic saline infusion in 8 patients with myxedema. The *shaded area* represents the range of values observed in 15 healthy adults during the same test (22). The curve numbers correspond to patient numbers

Diagnosis of Myxedema Coma

Dr. Nicoloff has suggested that advanced age might be added to the three key diagnostic features of myxedema coma: altered mental status, defective thermoregulation, and a precipitating event (7). This is because of the special problems the elderly have in compensating for the changes associated with hypothyroidism described above as well as the increased prevalence of hypothyroidism in the elderly (23).

Altered mental status – need not be coma; decreased orientation increased lethargy, confusion, or even psychosis is sufficient. The altered mental status may be secondary to some other event, e.g., stroke, medication effect, sepsis, or CO_2 narcosis.

Defective thermoregulation – either absolute or relative hypothermia (e.g., sepsis with inappropriately normal body temperature).

Precipitating illness or event – assume that such an event has occurred; infection (pulmonary or urinary tract) should be assumed until excluded.

Age – most patients who present with myxedema are elderly; increased incidence of hypothyroidism and reduced thermogenesis contribute.

Common Preciptating Events for Myxedema Coma

• Infection	• CO_2 Narcosis
• Trauma	• Drug Overdose
• Stroke	• Diuretics
• Hypothermia	• Sedatives
• Hypoglycemia	• Tranquilizers

The diagnosis of myxedema coma is initially based on the history, physical exam, and lack of another clear explanation for the clinical picture. The presence of supportive laboratory tests is usually not available (or required) before treatment.

Management of Myxedema Coma

Once the diagnosis of myxedema coma is entertained, appropriate therapeutic measures should be initiated. "When in doubt, treat" is the classic adage endocrinologists learn early in training in discussions of myxedema coma. Since the mortality of myxedema coma is still said to be as high as 30 to 40% (24), it should be considered an endocrine emergency. Approaching the management this way means that many patients who are treated with a presumptive diagnosis of myxedema coma actually are subsequently found to be euthyroid. This approach to treat with a presumptive diagnosis is not thought to be dangerous for euthyroid patients since studies of giving intravenous levothyroxine to patients with nonthyroidal illness did not demonstrate any adverse effects (25). If the patient under consideration does have myxedema coma, prompt appropriate therapy may be life saving.

Therapy should take place in an ICU setting. Baseline lab should include serum TSH, free T_4 estimate, cortisol, CBC with differential, and routine chemistries. Because of the likelihood of infection as a precipitating event, blood, sputum, and urine cultures should be obtained. It has been observed that few infected patients with myxedema coma have a WBC greater than 10,000. Thus, if bands are present or urinalysis, chest radiographs, or

sputum appearance is suspicious for infection, empiric broad spectrum parenteral antibiotics should be given.

Body temperature support – Myxedema patients are poikilothermic and may have their body temperature fall further if they are inadequately covered in an air-conditioned hospital setting. Passive rewarming is the appropriate approach to avoid vasodilatation and vascular collapse.

Respiratory support – Endotracheal intubation and ventilator assistance should be instituted at the first sign of repiratory failure. To further support oxygen delivery to tissues and hypoxemia administration of packed RBCs should be considered if the hematocrit falls below 30%.

Cardiovascular support – Any fall in blood pressure is ominous; look for silent gastrointestinal bleeding, myocardial infarction, overdiuresis, or iatrogenic vasodilatation from active rewarming.

Endocrine support – Autoimmune thyroid disease causing hypothyroidism may be accompanied by autoimmune adrenal insufficiency, and hypopituitarism may include secondary adrenal insufficiency as well as secondary hypothyroidism. Thus it is important to administer hydrocortisone 100mg every 8 hours until the baseline serum cortisol is confirmed to be at a level appropriate for stress.

Thyroid hormone therapy – The traditional therapy for myxedema coma since its description in 1964 (26) has been high dose intravenous sodium levothyroxine. The introduction of this therapy has been attributed with the decrease from the previous 50 to 80% mortality with the prior high dose triiodothyronine therapy (27). The usual initial dose is 300 to 500μg as an intravenous bolus followed by 50 to100μg daily. The range in dosage is meant to allow adjustment for the patient's weight, age, and the likelihood of complications such as myocardial infarction or arrhythmia. The lower range of dosage should be given to the lighter and older patients and those thought to be at risk for cardiovascular complications. The medication is given intravenously because of likely poor absorption due to myxedema of the bowel. The daily maintenance dose can be switched to oral when the patient has improved sufficiently. Although some authors prefer to give triiodothyronine (28-30) or a combination of T_4 and T_3 (24, 31), there is insufficient evidence of the safety and efficacy of such regimens. Since T_3 is the active thyroid hormone at the nuclear receptor and since T_4 to T_3 conversion is impaired in illness, it is intellectually appealing to consider giving T_3 to try to stimulate recovery more rapidly. A recent review of the outcome of treatment of 87 patients from the literature attempted to correlate mortality and the dose of T_4 and T_3 initially administered and suggested that doses of $T_4 \geq 500\mu g$ or $T_3 \geq 75\mu g$ were associated with an increased risk of mortality (Figure 5) (32). Similar to a previous report looking at risk factors for mortality (27), advanced age was also a predictor of a fatal outcome. It would make little sense to give T_3 alone since T_4 as a source of a continuous supply of serum T_3 will be needed. Although their recommendation for combined T_4 and T_3 therapy in myxedema coma is without reference to the literature, Drs. Ross and Wartofsky's alternative therapy

is appealing (24,31). They recommend 200 to 300μg T_4 as an intravenous bolus followed by 50μg daily. Simultaneously T_3 is given intravenously with an initial dose of 5 to 20μg followed by 2.5 to 10μg every 8 hours depending on the patient's age and cardiac risk factors.

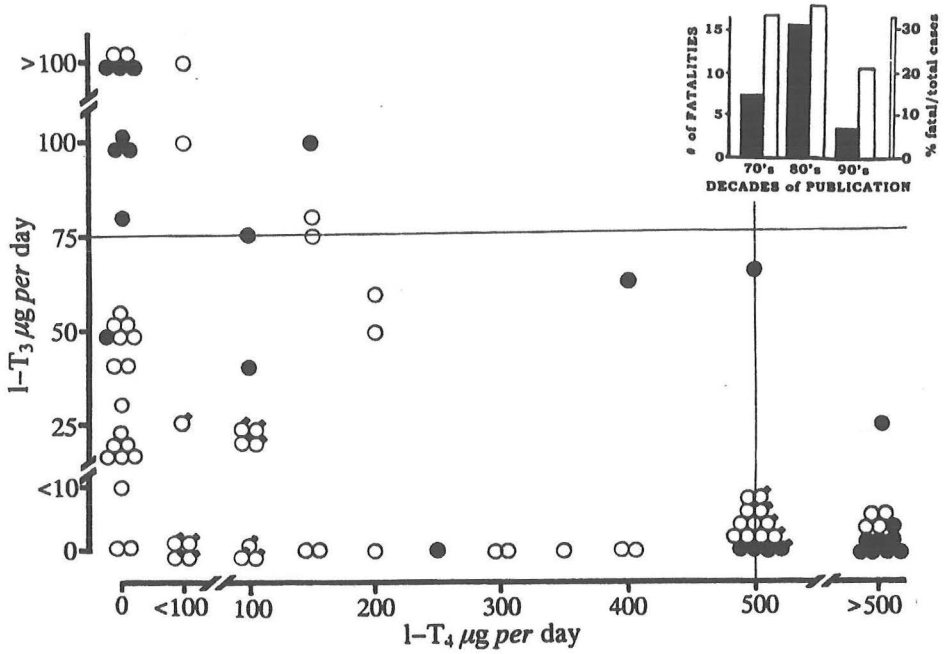


Figure 5 The relationship of the early treatment and the short-term outcome. The status of the patients, life or death, within 1 month of treatment were plotted against maximal dose per day of thyroid hormones in the first 3 days of treatment. Deceased patients are shown by closed circles and patients who survived by open circles. Circles with or without cubicles on the circumferences indicate parenteral or oral administration of levothyroxine (LT_4) respectively. The small diagram in the right upper quadrant shows the numbers (solid columns) and fractions (open columns) of fatal and fatal/total reported cases in the three decades in which cases were reported.

Levothyroxine loading leads to acute hemodynamic effects with increased cardiac index in one to two days (33). TSH levels fell 32% within the first 24 hours of a 428μg intravenous levothyroxine bolus, and serum T_3 levels rose significantly on the third day (34). The reversal of the blunted ventilatory responses occurs in seven days (Figure 6) (15).

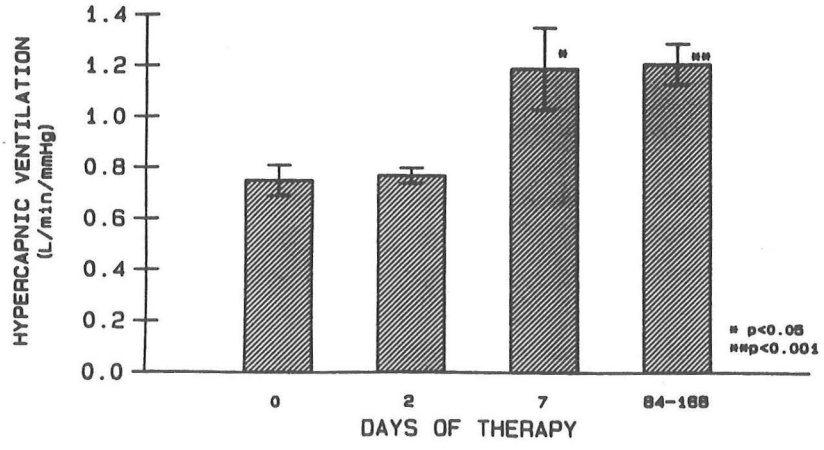


Figure 6 ***Top, reversal of abnormal hypercapnic ventilation (n = 10) by short-term parenteral T4 or T3 therapy, and by long-term oral L-thyroxine administration. Patients were reassessed after two (n = 8), seven (n = 9), and 84 to 168 days (n = 6) of therapy.***

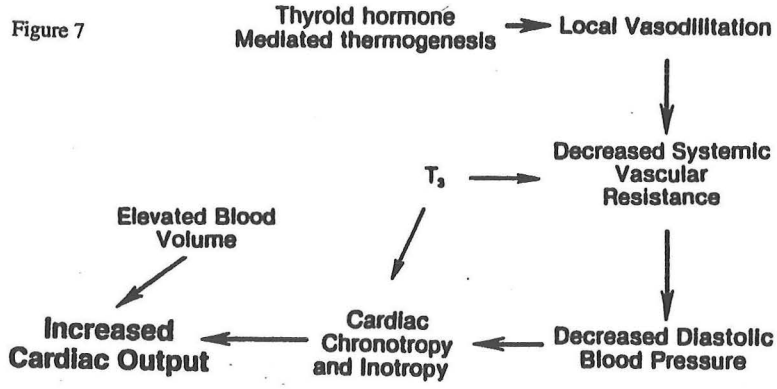
Thyroid Storm

Thyroid storm is the term commonly used to describe life-threatening thyrotoxicosis. It occurs when worsening of the effects of thyroid excess surpasses the patient's ability to maintain adequate metabolic, thermoregulatory, and cardiovascular compensatory mechanisms. There are no defining criteria or hormone levels for thyroid storm, but fever, mental status changes, evidence of multisystem involvement, and a precipitating event are usually seen (35).

Physiologic Adaptations to Hyperthyroidism

The physiologic adaptations to hyperthyroidism are in general the exact opposite to the changes seen in hypothyroidism. The increased metabolic rate stimulates enhanced blood flow to the tissues by vasodilatation (Figure 7) (9). The systemic vascular resistance is decreased by as much as 50%. Studies in isolated vascular smooth muscle cells demonstrated a direct effect of T_3 to cause cellular relaxation (36). This action of T_3 appears to be by a nongenomic mechanism based on the rapidity. The effect did not seem to involve endothelial cells since nitric oxide production was unchanged. And there were no changes in cyclic nucleotides in the vascular endothelial cells in response to T_3 stimulation to suggest second messengers. There was also no change in myosin light chain phosphorylation. The *in vivo* regulation of systemic vascular resistance likely involves a complex interaction of vasoactive substances capable of directly and indirectly altering smooth muscle tone. The bolus administration of T_3 to a sheep model demonstrated a rapid improvement in cardiac function without an increase in oxygen consumption that was caused by a decrease in afterload (37).

Figure 7



The decreased systemic vascular resistance leads to decreased diastolic blood pressure that enhances the rate and force of cardiac contraction. Sinus tachycardia is usually seen in severe thyrotoxicosis, and 15% of patients have atrial fibrillation. Myocardial contractility is also stimulated directly by thyroid hormone effects on several cardiac genes as mentioned above. Sarcoplasmic reticulum calcium-activated ATPase, Na/K-ATPase, and phospolambin are important examples (38). The end result is a stimulation of cardiac output by two- to three-fold. The stimulatory effects of thyroid hormone on red

blood cell production both directly and via stimulation of erythropoietin result in an increased blood volume.

The importance of the decreased vascular resistance to the increased cardiac function in thyrotoxicosis can be seen in two very different types of studies. Phenylephrine infusions were given to 7 normal subjects and 7 thyrotoxic patients following atropine (39). During phenylephrine infusions the increases in mean arterial and mean right atrial pressures in the thyrotoxic patients did not differ appreciably from those of the normal subjects. Reductions in heart rate were small and not significantly different in the two groups. Significant dose-related decreases in cardiac output occurred in the thyrotoxic patients but not in the normal subjects. The decrease in cardiac output in the thyrotoxic patients was likely due to vasoconstriction, suggesting that the increased cardiac output in thyrotoxicosis is partly secondary to peripheral vasodilatation. In the second study the effects of thyroid hormone on cardiac size and myosin content were evaluated in a heterotopically transplanted rat heart model (40). Thyroid hormone administration led to a significant 30% increase in total heart weight and a 40% increase in the myosin content of the in situ heart when compared to the control. In contrast, T_4 treatment was without effect on the heart weight, protein content, or myosin content of the heterotopic, nonworking heart. There was a shift in myosin isozyme expression in the heterotopic hearts in response to thyroid hormone, and thus myosin isoenzyme expression can be altered by changes in workload but is still responsive to increased levels of thyroid hormone.

Hyperthyroidism and Apparent Catecholamine Excess

The hemodynamic changes of hyperthyroidism as well as the diaphoresis and tremor suggest catecholamine excess. *In vitro* studies have demonstrated thyroid hormone enhacement of catecholamine receptor numbers in a number of tissues. However, attempts to demonstrate enhanced sensitivity to catecholamines *in vivo* have not supported such an effect. Cryer's group measured target tissue β-adrenergic receptor density and metabolic and hemodynamic sensitivity to eplinephrine *in vivo* in normal humans before and after administration of triiodothyronine (100 μg daily) for 10 days (41). Despite increments in β-adrenergic receptor densities in fat (~60%) and skeletal muscle (~30%) and probably other target tissues, metabolic and hemodynamic sensitivity to epinephrine *in vivo* was unaltered. Direct measurements of serum levels of catecholamines in spontaneously hyperthyroid patients demonstrate values that are equal to or less than normal. Some investigators have suggested that thyroid hormones and catecholamines may share a common pathway to produce various cellular effects (reviewed in 42). As a result of structural similarities between thyroid hormone and catecholamines, it has been suggested that when serum levels of thyroxine are increased the hormone is taken up, partially metabolized, and subsequently released at the level of the synapse serving as a sympathomimetic transmitter. In any case it is hard to ignore the major role of β-adrenergic blockade in treatment of thyrotoxicosis, including decreasing or reversing tachycardia, widened pulse pressure, increased cardiac output, and palpitations (see below).

Diagnosis of Thyroid Storm

As mentioned above there are no absolute criteria for the diagnosis of thyroid storm. The absolute levels of thyroid hormones may vary from individual to individual. However, one would postulate that the development of thyroid storm in a given individual should be should be associated with increased levels of free thyroid hormones. Drs. Burch and Wartofsky have developed a scoring system to standardize interpretation of the medical literature in regard to thyroid storm (35). The scoring system is not for clinical use but is helpful to review the clinical manifestations of thyroid hormone excess.

Drs. Burch and Wartofsky's Diagnostic Point Scale for Thyroid Storm

For patients with severe hyperthyroidism identify within each of the five categories the patient's parameter with the highest number of points; add points from all categories.
If the total number > 44, highly suggestive for thyroid storm;
25-44 suggestive, < 25 unlikely

Thermoregulatory Dysfunction		
Temperature	99-99.9	5
	100-100.9	10
	101-101.9	15
	102-102.9	20
	103-103.9	25
	≥ 104	30
CNS Effects		
Agitation		10
Delirum, psychosis, stupor		20
Seizure, coma		30
GI/Liver Dysfunction		
Diarrhea, N,V, Abd pain		10
Unexplained jaundice		20
Cardiovascular Dysfunction		
Heart Rate	90-109	5
	110-119	10
	120-129	15
	130-139	20
	≥ 140	25
CHF	Pedal edema	5
	Bibasilar rales	10
	Pulmonary edema	15
Atrial Fibrillation		10
Precipitant History		
Positive		10

When the above scoring system was applied retrospectively to 61 cases of thyroid storm reported in the literature, the point scale identified 59 cases as thyroid storm (35). The known precipitants of thyroid storm can be categorized into:

Conditions associated with a rapid rise in thyroid hormone levels – thyroid surgery, withdrawal of antithyroid drug therapy, radioiodine therapy, iodinated contrast dyes, and vigorous palpation of the thyroid.

Conditions associated with acute or subacute nonthyroidal illness – nonthyroidal surgery, infection, cerebrovascular accident, pulmonary embolism, diabetic ketoacidosis, trauma, and parturition.

Since the thyroid hormone changes associated with serious nonthyroidal illness usually involve an increase in the free fraction of the circulating thyroid hormones (43), all of the precipitants listed above could be viewed as mechanisms to increase free thyroid

hormone levels. Indeed small case series and individual case reports would seem to support the presence of increased free thyroid hormone levels in patients with storm compared with patients without storm (44,45). In the small series, six patients with thyroid storm were compared with six patients from a group of 15 with uncomplicated thyrotoxicosis selected solely on the total T_4 level being similar to the thyroid storm patients (44). While the total T_4 levels were similar, the dialyzable fraction and free T_4 concentrations were higher in the thyroid storm group (Figure 8). Although these findings are useful in understanding the pathophysiology, a certain value for the free T_4 or free T_3 in an individual does not define thyroid storm.

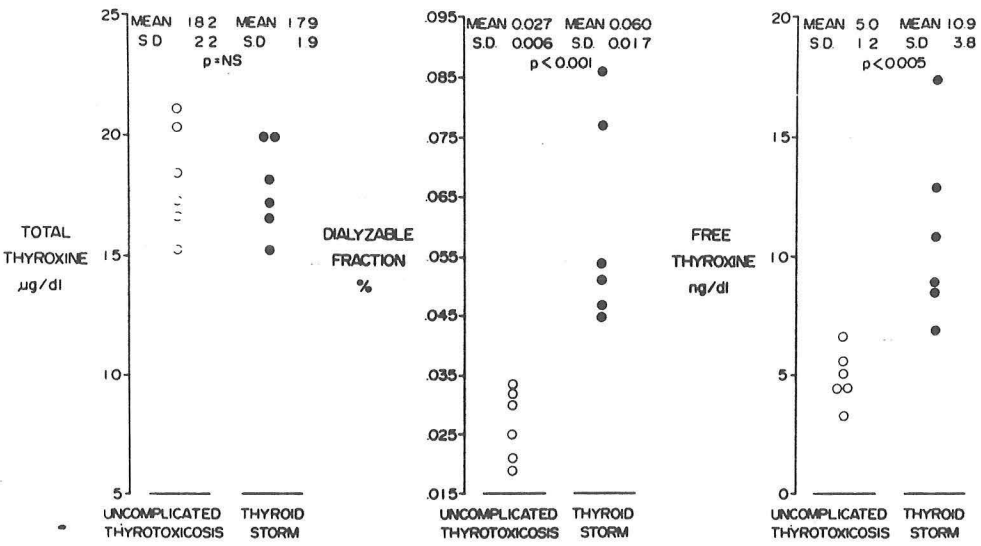


Figure 8 Total thyroxine, dialyzable fraction, and free thyroxine levels of patients with uncomplicated thyrotoxicosis matched to patients with thyroid storm solely from T4 values. Thyroid storm is characterized by the combination of a high dialyzable fraction and a high free thyroxine level. NS = not significant.

Heart Failure in Thyroid Storm

Thyrotoxicosis has been thought to cause heart failure in a subset of patients (46-48). Sandler and Wilson observed evidence of cardiac disease in 150 out of 462 patients being treated with radioiodine (46). Clinical manifestations of heart disease occurred concomitantly with prior ischemic, hypertensive, or valvular pathology in 57% of the patients. Atrial arrhythmias and/or congestive heart failure were noted in 43% of subjects without evidence of associated or underlying heart disease. This group could be viewed as having thyroid heart disease. Of the patients with thyroid heart disease, the prevalence of clinical findings increased with age: 75% had atrial fibrillation, 20% had cardiomegaly, and only 5% had evidence of congestive heart failure without and accompanying supraventricular arrhythmia. The major hemodynamic finding that distinguishes thyrotoxic patients with heart failure from those free of cardiac symptoms is a higher level of SVR (compared with the usually low levels of SVR in thyrotoxicosis) (47,48). With exercise the level of SVR rises disproportionately (48). In one study hyperthyroid patients failed to demonstrate the expected rise in LVEF with exercise but did so after a returning to a euthyroid state (49). The failure to increase LVEF with exercise in some hyperthyroid patients may be due to an inability to further lower SVR beyond an already markedly reduced value (47).

In the absence of atrial fibrillation, heart failure due to thyrotoxicosis itself is uncommon. In younger patients or in the absence of underlying heart disease, heart failure associated

with hyperthyroidism is thought to be "high output failure". High output failure may not be true heart failure but rather reflect a congested circulation caused by excess sodium and fluid retention. Hyperthyroid patients with normal cardiac function may have expanded blood volumes with increased venous filling pressures and peripheral edema. The hypothesis invoked to explain true heart failure in thyrotoxicosis is the observation that chronic persistent tachyarrhythmias can alter left ventricular contractility (50). This has been referred to as rate-related heart failure and is thought to result from the effect of sustained tachycardia impairing the ability of the ventricular myocyte to regulate calcium content. Thus patients with severe hyperthyroidism for the long periods of time would be at the highest risk for developing heart failure. The observation that cardiac function returns to normal with treatment of the thyrotoxicosis and the atrial fibrillation confirms the importance of rate control and supports tachyarrhythmias as the etiologic mechanism in the heart failure (50).

Management of Thyroid Storm

The treatment of thyroid storm should take place in an ICU setting. A search should be made to identify the precipitating event in order to avoid further contribution of a given mechanism of decompensation. Although the levels of free thyroid hormones may not be useful in diagnosis, they can serve as a baseline.

The management of thyroid storm can be viewed as having four components (35):
1) Reduce additional contributions of thyroid hormone from the thyroid gland
2) Minimize end-organ effects of thyroid hormone
3) Reduce chances of systemic decompensation
4) Treat precipitating event

Treatment directed against the thyroid gland –

Inhibition of new thyroid hormone synthesis with thionamide drugs.There are two thionamide drugs: propylthiouracil (PTU) and methimazole (MMI). Both block organification of iodine into thyroid hormones, but PTU offers the additional benefit of inhibiting T_4 to T_3 conversion in liver and kidney. If PTU is given, it should be initiated with an oral loading dose of 1000 mg followed by 200-250 mg every 4 hours. For patients who are unable to ingest or keep down oral PTU, the same doses may be given rectally (51). PTU is administered every 4 hours because of its relatively short half-life. Although such a regimen should not be a problem in the ICU, given the possibility of tests or errors delaying dosing, Dr. Ross has argued a preference for use of methimazole as long as a separate inhibitor of T_4 to T_3 conversion is used (52). Methimazole can be given at a dose of 30 mg every 6 hours. It may also be given rectally (53). The longer half-life of methimazole offers a safety margin if doses are delayed. Sodium ipodate and iopanoic acid are agents originally used for oral cholecystograms that happen to be potent inhibitors of T4 to T3 conversion in all tissues. They have structural similarity to thyroxine and have been shown to be effective in the rapid control of thyrotoxicosis (54,55). Sodium ipodate is the agent most commonly reported for this use. Iopanoic acid

is the one we have on the PMH formulary. The dose is the same for either agent, 1 gram daily.

Inhibition of thyroid hormone release with iodine or lithium. Blocking thyroid hormone release is usually accomplished with inorganic iodine which directly inhibits colloid proteolysis and release of T_4 and T_3 from the thyroid. Lugol's solution (8 drops) or saturated solution of potassium iodide (SSKI) (6 drops) is given orally every six hours or diluted and given as a retention enema (51). Iopanoic acid and sodium ipodate also release stable iodine with each 500 mg capsule containing 308 mg of iodine. The dose of either agent is 1 gram daily. It is important in giving either stable iodine or the organic iodine preparations to wait an hour after the administration of the thionamide drugs to allow time to establish a block in organification; otherwise the iodine might serve as a substrate for making more thyroid hormone. Lithium carbonate (initially 300 mg every 6 hours) may be substituted for iodine in patients with severe iodine allergy. The dose is then titrated to a serum level of 1 mEq/L. Significant renal and neurological toxicity impair lithium's usefulness.

Treatment directed against the peripheral effects of thyroid hormone –

Inhibition of T_4 to T_3 conversion by PTU and the radiographic contrast agents iopanoic acid and sodium ipodate has been discussed above. In all patients with thyroid storm it is recommended to also give pharmacological doses of glucocorticoids. Glucocorticoids block T_4 to T_3 conversion but also have an effect to separately improve Graves' disease, the usual thyroid disease associated with thyroid storm. Either hydrocortisone 100 mg every 8 hours or dexamethasone 2 mg every 6 hours should be given intravenously. The combination of PTU, iodides, and dexamethasone is extremely effective in lowering serum T_3 levels. In a report cited in Dr. Foster's rounds on this subject, this combination of drugs resulted in normalization of serum T_3 within 24 hours in severe thyrotoxicosis (56).

β-adrenergic blockade has been a major addition to the treatment of thyroid storm. In patients with severe tachyarrhythmias, β-blockers may be the most important category of medications to give first. Higher doses are required in thyroid storm. If needed to treat a rapid heart rate quickly, propranol is given intravenously at 0.5 to 1.0 mg initially with monitoring up to 2 to 3 mg in 15 minutes and 60 to 80 mg is also given orally every 4 hours (57). Alternatively intravenous esmolol can be used for short-acting rate control with a loading dose of 250 to 500 μg/kg followed by an infusion of 50 to 100 μg/kg per minute (58). Caution should be used in treating patients with moderate to severe congestive heart failure with β-blockers. Propranol is known to have a greater depressant effect on myocardial contractility in the hyperthyroid heart. In the setting of severe congestive heart failure β-blocker use should primarily be limited to correcting the tachyarrhythmia possibly contributing to the heart failure. Propanolol is also contraindicated in patients with asthma; guanethidine or diltiazem can be used (59,60).

Removal of excess circulating thyroid hormone can be accomplished by plasmapheresis or charcoal plasma perfusion (61).

Treatment directed against systemic decompensation – Acetaminophen and cooling blankets should be used for hyperthermia. Aspirin should be avoided because of the potential effect of displacing thyroid hormones from binding proteins. Fluids may be needed at a rate of 3 to 5 liters per day. Because of the depletion of liver glycogen and usual thiamine deficiency, fluids should contain glucose and thiamine. Congestive heart failure may require close monitoring of fluid therapy and administration of diuretics. Thyrotoxic patients require larger than usual doses of digoxin. As mentioned above glucocorticoids are routinely given in thyroid storm. Most experts feel that the additions of glucocorticoids improves survival (35). One report of cortisol levels in thyroid storm patients comments that the levels were just normal but not elevated as would be expected for the stress of the illness (59).

Treatment directed against the precipitating event – All febrile patients should be cultured. The routine use of broad spectrum antibiotics is not recommended unless there is evidence in addition to fever to suggest infection (35). In some individuals no precipitant can be identified even in retrospect (59).

Thyroid storm is said to have a mortality of 20 to 30% (62). We encounter patients with thyroid storm more frequently in our Parkland population than would be expected from descriptions of frequency of the disorder in the literature. An assessment of the clinical and socioeconomic predispositions to complicated thyrotoxicosis identified several factors: noncompliance with prescribed treatment for thyrotoxicosis, pre-existing organ system disease, being uninsured or covered by Medicaid, and having a thyroxine greater than twice the upper limit of normal (63). My impression is that the experience in treating this condition in our hospital has resulted in a lower mortality.

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