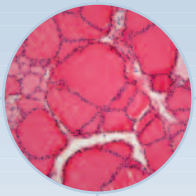

Hypothyroidism and Myxedema Coma

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ABSTRACT: Hypothyroidism is a common endocrinopathy in dogs but is rare in cats. Lymphocytic thyroiditis and idiopathic thyroid atrophy are common causes of this condition. Specific thyroid function tests, in conjunction with clinical signs and physical examination findings, are used to help confirm a diagnosis of hypothyroidism. This disease can be managed with synthetic hormone supplementation and has an excellent prognosis. Myxedema coma is a rare and potentially fatal manifestation of severe hypothyroidism that can be successfully treated using intravenous levothyroxine.

Hypothyroidism is a frequently diagnosed endocrinopathy in dogs[1,2] but a rare phenomenon in cats.[1] The thyroid, under the influence of thyrotropin (thyroid-stimulating hormone [TSH]), produces the hormones thyroxine (T_4) and 3,5,3'-triiodothyronine (T_3). T_4 and T_3 have many effects on cellular metabolism, and their levels in the body are tightly regulated. Dysregulation of T_3 and T_4 levels has far-reaching effects. The signs of thyroid hormone deficiency are vague, nonspecific, and not pathognomonic. No single test can be conducted to make a definitive diagnosis. Instead, a diagnosis of hypothyroidism is made based on a combination of clinical signs, physical examination findings, biochemical abnormalities, and thyroid function tests. With this combination of tests, a diagnosis of hypothyroidism can be made with confidence. However, clinicians must keep in mind that nonthyroidal illness, some medications, physical activity level, and antithyroglobulin antibodies can alter the results of thyroid function tests. Once a diagnosis has been made, this disease can be easily controlled with thyroid hormone supplementation. A rare but serious complication of severe hypothyroidism is myxedema coma.

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PHYSIOLOGY

Iodine and tyrosine are the basic substrates involved in thyroid hormone synthesis (Figure 1). Dietary iodide is actively transported into thyroid follicular cells and oxidized to iodine by thyroperoxidase. Iodine then binds to tyrosine residues on thyroglobulin to form monoiodotyrosine (MIT) and diiodotyrosine (DIT). Coupling of MIT and DIT forms both T_3 (MIT–DIT) and T_4 (DIT–DIT), which are bound to thyroglobulin and stored in colloid. Under the control of TSH, thyroglobulin undergoes proteolysis in phagolysosomes, releasing T_3 and T_4.[3,4] Thyroid hormones are water-insoluble, and their ability to circulate

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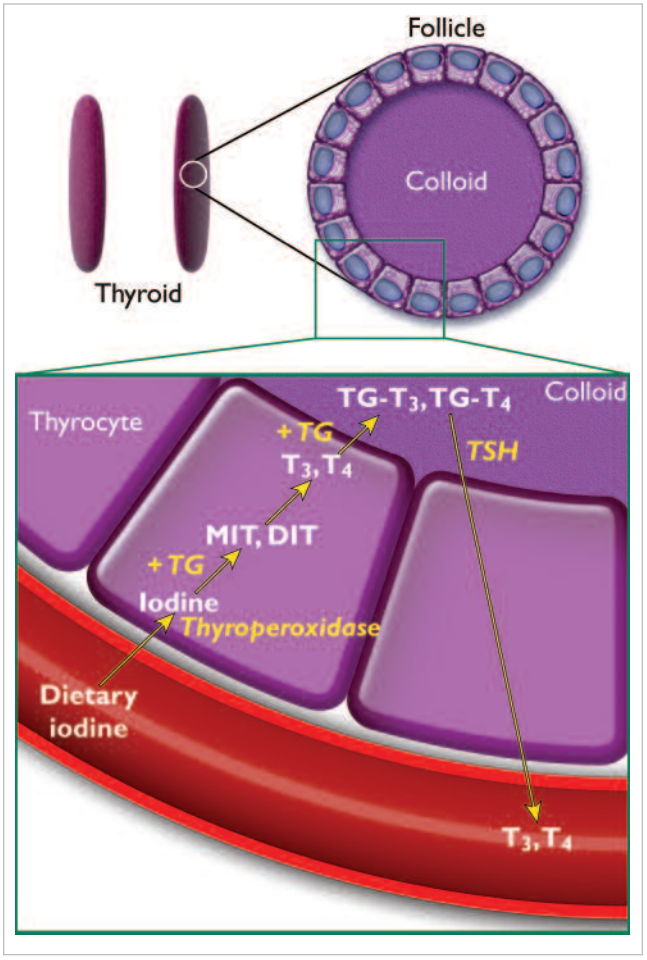


Illustration by Felecia Paras

Figure 1. Thyroid hormone synthesis. Iodine is transported into thyroid follicular cells and oxidized. It binds to tyrosine residues and forms monoiodotyrosine *(MIT)* and diiodotyrosine *(DIT)*. MIT and DIT combine to form T_3 (MIT–DIT) and T_4 (DIT–DIT), which are bound to thyroglobulin *(TG)* for storage. Under the influence of thyroid-stimulating hormone *(TSH)*, TG undergoes proteolysis, and T_3 and T_4 are released.

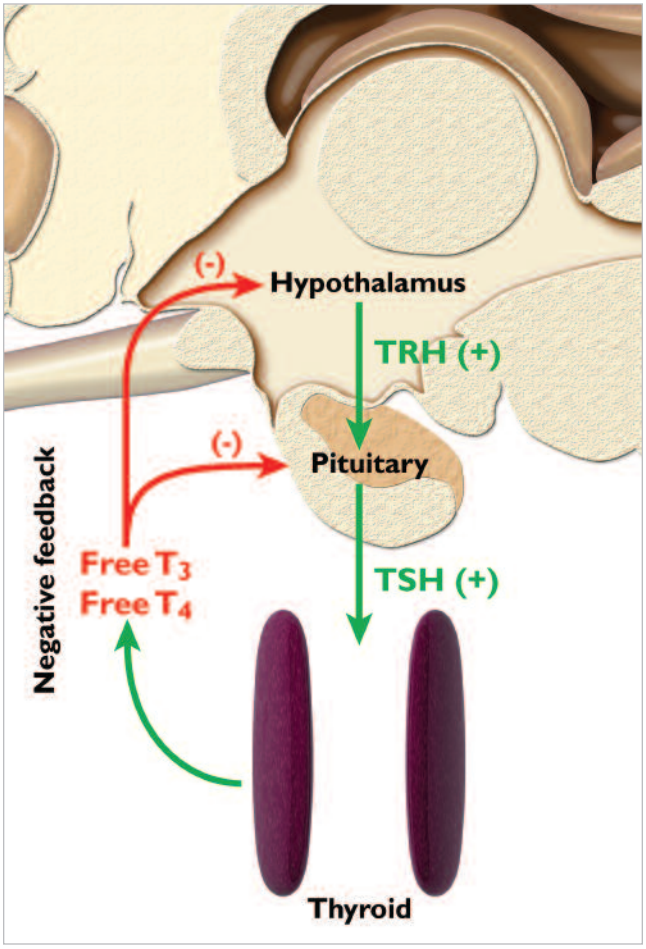


Illustration by Felecia Paras

Figure 2. Production and release of thyroid hormone. The hypothalamus produces thyrotropin-releasing hormone *(TRH)*, which stimulates the anterior pituitary to produce TSH, which then stimulates the thyroid. TRH and TSH production is down-regulated by circulating thyroid hormones, particularly T_3.

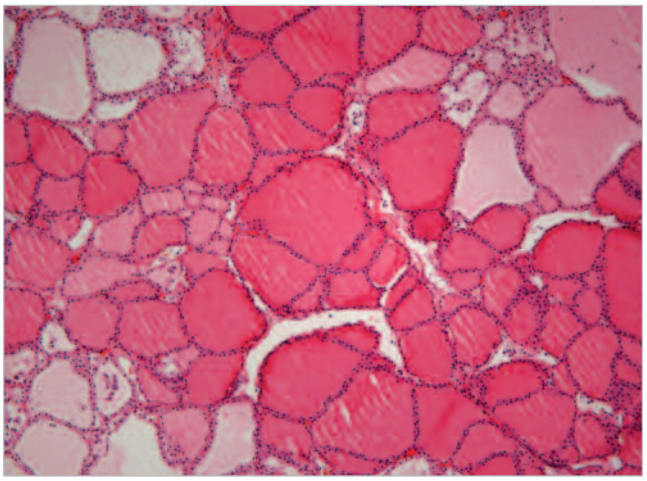
depends on binding to T_4-binding globulin, T_4-binding prealbumin, or albumin. Most thyroid hormone (i.e., >99%) is protein bound, with the remaining unbound portion being the metabolically active or "free" form.[3–5] These binding proteins are reservoirs for circulating thyroid hormone and allow the free hormone level to be maintained within a very narrow range. T_4 is the main secretory product of the thyroid. However, T_3 is more biologically active and is most effective in binding to and activating the thyroid hormone nuclear receptor. Once in peripheral tissues, T_4 is deiodinated to T_3 before receptor binding. Most T_3 (i.e., 40% to 60%) is derived from extrathyroidal deiodination of T_4.[3,4]

The production and release of thyroid hormones are controlled by a classic negative feedback mechanism (Figure 2). The hypothalamic–pituitary–thyroid axis is responsible for maintaining control of extrathyroidal hormone levels. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates thyrotropes in the anterior pituitary to produce TSH. In addition to hormone release, TSH stimulates growth of the thyroid gland.[4] Thyroid hormones, particularly T_3, provide feedback to the hypothalamus and pituitary to down-regulate TRH and TSH production.

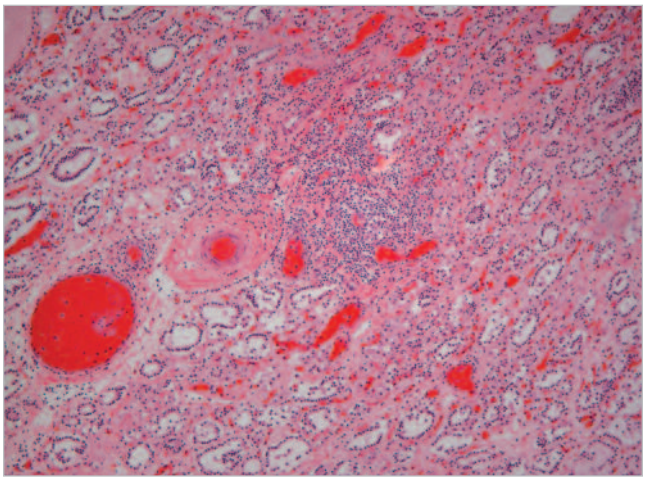
PATHOPHYSIOLOGY

Hypothyroidism can be classified as acquired or congenital. Acquired hypothyroidism can be primary, sec-

Figure 3. Canine thyroid tissue (magnification ×10). (Courtesy of Serena M. Liu,VMD, MS, DACVP, The Animal Medical Center, New York, NY)



Normal tissue with colloid-filled follicles.



Mild lymphocytic thyroiditis. Infiltration of lymphocytes results in the destruction of the normal thyroid architecture.

ondary, or tertiary and usually affects adult dogs, with the average age at diagnosis being 7 years.[2] Primary hypothyroidism is associated with a defect localized to the thyroid. With this form of hypothyroidism, the thyroid tissue has been destroyed or replaced and thus becomes less responsive to TSH. Therefore, T_3 and T_4 levels gradually decline, with a compensatory increase in TSH (Figure 3).

There are two common histologic forms of primary hypothyroidism: The first, lymphocytic thyroiditis, is thought to be an immune-mediated process and eventually results in thyroid atrophy. The second, idiopathic thyroid atrophy, is a separate form of thyroid destruction that does not demonstrate an inflammatory component.[6] Together, these processes account for 95% of the clinical cases of hypothyroidism in dogs.[7] This is comparable with humans, in which 99% of hypothyroidism is the result of these mechanisms.[8] In dogs, lymphocytic thyroiditis and idiopathic thyroid atrophy each accounts for half of the reported cases.[6,7] Lymphocytic thyroiditis is characterized by chronic and progressive lymphocytic infiltration and destruction of the thyroid. Cytotoxic T cells set up inflammation, leading to thyrocyte destruction and parenchymal fibrosis.[1,6] This process is gradual and accounts for the slow onset of clinical signs associated with hypothyroidism. The immune-mediated process is associated with production of autoantibodies, predominantly against thyroglobulin.[1,9,10] However, autoantibodies against T_3 and T_4 have been reported.[11,12] Although T_3 and T_4 are haptens, they are attached to thyroglobulin, which appears to act as the antigenic stimulus for antibody production.[11] This differs from the process in humans, in which the immune target is thyroperoxidase.[8] Recent vaccination may cause an elevation in antithyroglobulin antibodies unassociated with primary hypothyroidism.[13] Autoantibodies crossreact with T_4 assays.[1,14] This is clinically important because when autoantibodies are present, the total serum T_4 level can be elevated into the reference or hyperthyroid ranges, causing clinicians to miss a diagnosis of hypothyroidism.[1,15] Idiopathic thyroid atrophy results in replacement of normal tissue with adipose tissue.[6] Rare causes of primary hypothyroidism include neoplastic destruction of thyroid tissue, iodine deficiency, infection, and iatrogenic destruction secondary to drugs, surgery, or radioiodine treatment.[1,2,16,17]

Secondary and tertiary hypothyroidism are rare.[1] In secondary hypothyroidism, the defect is localized to the pituitary, and the ability to synthesize and secrete TSH is impaired. Secondary hypothyroidism may be caused by pituitary tumors, congenital malformation of the pituitary, infection, or TSH suppression.[1,2] TSH suppression can be caused by drugs, hormones, or concurrent illness.[1,2,18] Tertiary hypothyroidism is hypothalamic in origin,[8] and production of TRH is either decreased or nonexistent. Tertiary hypothyroidism has not been reported in the veterinary literature.[19] Both secondary and tertiary hypothyroid patients would be expected to

Clinical Signs of Canine Hypothyroidism[23]

Common (40%–49% of clinical cases)
- Obesity
- Alopecia
- Lethargy

Uncommon (9%–15% of clinical cases)
- Pyoderma
- Dry haircoat
- Bradycardia

Rare (<5% of clinical cases)
- Facial nerve paralysis
- Hyporeflexia
- Vestibular disease
- Keratoconjunctivitis sicca
- Polyneuropathy
- Conjunctivitis

demonstrate increased thyroid hormone levels in response to TSH or TRH stimulation, respectively.

Congenital hypothyroidism, which is rare in veterinary medicine, is caused by inherited defects or by exposure of the fetus or newborn to either an excess or a deficiency of dietary iodine.[20] Congenital hypothyroidism is categorized as goitrous or nongoitrous. *Goiter*, the term for enlargement of the thyroid, develops when there is increased release of TSH, along with an intact thyroid TSH receptor.[3,20] Clinical signs of congenital hypothyroidism include developmental delays, both mental and physical, and dwarfism. An autosomal recessive form of congenital hypothyroidism has been reported in toy fox terriers,[20] giant schnauzers,[21] and Abyssinian cats.[22] Affected animals have a thyroid peroxidase deficiency. Genetic testing is available to detect carrier fox terriers.[2,20] Congenital hypothyroidism is also noted as an element of panhypopituitarism.[2]

CLINICAL SIGNS AND ROUTINE BLOOD ANALYSIS

Clinical signs associated with hypothyroidism are vague and involve many different systems (see box on this page). The most commonly reported clinical signs include dermatologic abnormalities, weight gain, lethargy, and weakness.[23] Most changes appear to be secondary to decreased metabolism due to a lack of circulating thyroid hormones.

Dermatologic changes, including alopecia, seborrhea, and pyoderma, are commonly associated with hypothyroidism. However, changes in the epidermis and haircoat are often breed specific[24,25] and are not noted in every patient. The value of skin biopsies is controversial[1] because many cutaneous changes are nonspecific and biopsy specimens from different endocrinopathies may demonstrate similar changes.[24] However, certain findings, including dermal thickening, myxedema, and vacuolation of arrector pili muscles, are most characteristic of hypothyroidism.[24] Bilateral symmetric nonpruritic truncal alopecia is reported in 88% of hypothyroid dogs.[23] Thyroid hormones are required for initiation of anagen (active hair growth). In hypothyroid animals, most hair follicles are retained in telogen (i.e., the quiescent or resting phase of the hair cycle). Without thyroid hormones, the haircoat becomes dry, dull, and brittle. Hair loss is noted in areas of increased wear and usually includes the ventral thorax and neck, ventral abdomen, and tail. Loss of primary hair is most common with retention of guard hairs, resulting in a short, fine haircoat.[19,23] Hyperpigmentation may be noted in areas of alopecia.

Other skin changes include dry scaly skin, pyoderma, dermatitis, seborrhea, hyperkeratosis, myxedema, and otitis externa. Thyroid hormone enhances the lymphoid immune response.[26] In the hypothyroid state, there is decreased T-cell function and humoral immunity.[1] This decrease in local immunity causes the skin to become more susceptible to infection. Pyoderma has been reported in 14% of dogs with hypothyroidism.[23] Generalized demodicosis and *Malassezia* spp infections are common.[24] An increased incidence of otitis externa also tends to be noted compared with the incidence in nonhypothyroid dogs. Primary dermatologic conditions such as alopecia, dry skin, and seborrhea are nonpruritic, but pruritis often accompanies secondary parasitic, yeast, or bacterial infection.[1,24]

Neurologic abnormalities are rare. Most neurologic signs are associated with polyneuropathy and include weakness, facial nerve paralysis, vestibular signs (usually peripheral), and hyporeflexia. Segmental demyelination and axonopathy are the likely pathogenesis of these clinical signs.[27,28] Megaesophagus and laryngeal paralysis have both been suggested to be associated with hypothyroidism; however, no data support this association.[23,29] A causal relationship between hypothyroidism and myasthenia gravis has not been proven.[30,31] Central nervous system signs, including seizures, ataxia, behavior changes, and coma, are rare. They may result from myxedema, lack of thyroid hormone, hyponatremia, or decreased blood flow to the brain.[1,32,33]

Several reproductive abnormalities have been suggested to be associated with hypothyroidism. In males, these include decreased fertility, testicular atrophy, poor semen motility, and decreased libido.[1] In females, hypothyroidism has been suggested to be associated with pro-

longed interestrous periods, failure to cycle, decreased libido, and inappropriate mammary gland development.[1] No data have supported an association between decreased thyroid hormone levels and reproductive failure in males or females.[34,35] When reproductive failure is detected, causes besides hypothyroidism must also be investigated.

Cardiovascular abnormalities, although rare, have been reported. Cardiovascular signs may be secondary to problems with conduction or direct myocardial effects. Bradycardia, arrhythmias, decreased conduction, decreased contractility, and diastolic dysfunction have been reported.[23] In the hypothyroid state, there is a decreased β-adrenergic receptor number, accounting for decreased contractility and lower heart rates.[36] In contrast to humans, congestive heart failure has not been documented secondary to hypothyroidism in dogs.[37]

Ocular changes can include corneal cholesterol deposits, keratoconjunctivitis sicca, and conjunctivitis, although these signs are reported in less than 1% of all hypothyroid dogs.[23]

Hypercholesterolemia, hypertriglyceridemia, and hyponatremia are commonly noted in serum biochemistry results[29,38] (see box on this page). These changes are the result of the decrease in normal lipid metabolism accompanying hypothyroidism. Hypothyroid dogs have increased very–low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins.[39] Increased triglyceride levels may play a role in the development of pancreatitis, although this association has not been proven. Elevated levels of cholesterol and triglycerides have been associated with atherosclerosis in dogs, although this is rare.[39,40]

Anemia is another common finding, affecting 28% to 32% of hypothyroid dogs.[31,38] The anemia is usually normochromic, normocytic and nonregenerative and likely results from one of or a combination of three mechanisms: There may be decreased erythropoietin production, a reduced response of progenitor cells to erythropoietin, or decreased stimulation of early hematopoietic stem cells.[41] The hypothyroid state does not affect the erythrocyte life span.

Common Laboratory Findings Associated with Hypothyroidism

Serum biochemical abnormalities
- Hypercholesterolemia
- Hyperlipidemia
- Hypertriglyceridemia
- Hyponatremia

Complete blood count abnormality
- Nonregenerative anemia (usually normochromic, normocytic)

THYROID FUNCTION TESTING

The diagnosis of hypothyroidism is complex. The TSH stimulation test is a reliable single test used to diagnose hypothyroidism and is considered the gold standard.[42] However, there is limited access to test reagents, and the cost is often prohibitive. Other tests are available to help clinicians evaluate thyroid function, thyroid hormone levels, and antithyroglobulin antibody levels. These tests include total T_4, endogenous canine TSH, free T_4, antithyroglobulin antibodies, anti-T_3 antibodies, anti-T_4 antibodies, total T_3, free T_3, and reverse T_3.

Assessment of total thyroxine as a screening test in combination with thyroid-stimulating hormone assessment as a confirmatory test are appropriate for obtaining a diagnosis of hypothyroidism. Free thyroxine may be used when initial test results are unclear.

A commonly requested initial screen of thyroid function is the total T_4 level test, which measures both protein-bound and free T_4 levels. The total T_4 level is a direct assessment of the functional ability of the thyroid tissue to produce hormone. A decreased total T_4 level is a common finding in hypothyroid animals; however, this is not diagnostic of hypothyroidism and necessitates more specific testing to confirm the diagnosis.[43] The total T_4 level can be measured by ELISA, chemiluminescence, or radioimmunoassay. There is indication that in-house ELISA is less reliable than radioimmunoassay.[44]

Measurement of the endogenous TSH level is available using a canine assay. Because of crossreactivity, this assay may also be used in cats.[45] In the hypothyroid state, the TSH level would be expected to be elevated due to loss of negative feedback. The TSH level test has high specificity and low sensitivity. Because total or free T_4 and TSH levels are both elements of the feedback

mechanism of the hypothalamic–pituitary–thyroid axis, they should be interpreted together. In other words, to accurately understand the significance of a TSH level, the clinician must know the total or free T_4 level. Current methods of assessing TSH levels are not sensitive at low levels. Therefore, TSH cannot be used in the diagnosis of secondary hypothyroidism.

The free T_4 level test measures the metabolically active portion of the total T_4 level. This fraction of the hormone can enter the cell, be converted into T_3, and interact with the thyroid hormone receptor. Hypothyroid animals would be expected to have a low free T_4 level. This test, like the total T_4 level test, is most valuable as a screening test. Concurrent illness has less effect on the free T_4 level compared with the total T_4 level.[43,46] However, glucocorticoids, phenobarbital, and hyperadrenocorticism have been noted to decrease the free T_4 level.[47–49] Different methods can be used to measure the serum free T_4 level. Measurement by equilibrium dialysis has been demonstrated to be the most reliable compared with radioimmunoassay.[50] The equilibrium dialysis method also mitigates the influence of antithyroglobulin antibodies, leading to the best likelihood of an accurate test result.

Immune-mediated thyroiditis may result in the production of antithyroglobulin or anti-T_3 or -T_4 antibodies. It is possible to test for antithyroglobulin antibodies, and a positive titer is predictive of immune-mediated thyroiditis[1,9,10] and suggestive of hypothyroidism.[51] Anti-T_3 and -T_4 antibodies may create a problem in the diagnosis of hypothyroidism. The antibodies are similar to those of T_3 and T_4 and can crossreact to falsely elevate assay levels.[10,15] Therefore, if anti-T_4 antibodies are present, the total T_4 level will reportedly be higher than it actually is. This is of most concern with animals in which the total T_4 level is truly just below the normal range. With the presence of anti-T_4 antibodies, these animals may actually appear to be euthyroid, thus delaying diagnosis and treatment of hypothyroidism. Free T_4 measured by dialysis is not affected by the presence of antithyroglobulin or anti-T_3 or -T_4 antibodies.[15] In some situations, the antithyroglobulin antibodies are positive, but the total and free T_4 levels are well within normal range, and the animal does not exhibit clinical signs associated with hypothyroidism. These cases demand close monitoring and reevaluation because they may be at risk of developing hypothyroidism.

For many years, the TSH stimulation test was used to diagnose hypothyroidism.[52,53] This test was routinely conducted using pharmaceutical-grade bovine TSH. With the introduction of recombinant human TSH, production of pharmaceutical-grade bovine TSH was halted. Studies[54,55] have demonstrated that recombinant human TSH can be used in both dogs and cats safely and effectively to conduct the TSH stimulation test. Adverse side effects of recombinant human TSH in humans include headache and nausea; no adverse effects have been reported in cats or dogs. Recombinant human TSH is very expensive, and although its use is validated, it is unlikely to become routine and displace the total and free T_4 tests and the TSH stimulation test as the preferred diagnostics.

Serum total T_3 measurement is an unreliable indicator of thyroid function. The total T_3 level has been demonstrated to be normal in up to 90% of all hypothyroid dogs.[46] In case-controlled studies, the reverse T_3 level has not been validated in companion animals. Therefore, evaluation of total T_3, free T_3, and reverse T_3 levels is not routinely recommended to assess thyroid function in dogs.[1,43]

Hypothyroidism is a common endocrinopathy in dogs and has vague clinical signs.

Another tool has recently become available to assist in the diagnosis of hypothyroidism. Two studies[56,57] have indicated that ultrasonography of the thyroid is helpful in distinguishing hypothyroid and euthyroid dogs. The studies demonstrated significant differences in thyroid volume and echogenicity between hypothyroid and euthyroid patients. There was no significant difference between euthyroid and sick euthyroid subjects. These studies concluded that ultrasonography can be an adjunctive diagnostic tool to assist in the diagnosis of canine hypothyroidism.[56,57] Limitations of this test include the need for high-quality ultrasonography equipment and a skilled, trained operator. In the future, this test may become more widespread and routine.

All available tests can be used to help diagnose hypothyroidism (Table 1). Investigation of hypothyroidism should be based on an increased index of suspicion. A complete blood count, serum biochemistry profile, and urinalysis are helpful in ruling out the pres-

Table 1. Available Tests for the Diagnosis of Hypothyroidism

Test/Tool	Measures	Affected By	Comments	Recommended
Total T_4	Protein-bound and free T_4	Antithyroglobulin antibodies may falsely increase the result	Low total T_4 level is suggestive but not diagnostic	Yes
		Other illnesses or drugs may falsely decrease the result (box on p. 27)	Radioimmunoassay is preferred	
Canine TSH	Endogenous TSH	—	Not sensitive at low TSH levels	Yes, with total and free T_4 levels
Free T_4	Free T_4	Drugs may falsely decrease results (box on p. 27)	Equilibrium dialysis method is preferred	Yes, with total T_4 or canine TSH levels
		Hyperadrenocorticism may falsely decrease the result		
Antithyroglobulin antibodies	T_3 or T_4 antibody levels	Presence of antithyroglobulin antibodies may increase the total T_4 level	Positive titer is suggestive of hypothyroidism	Yes, as an adjunct test in dogs with slightly low total T_4 levels
TSH stimulation test	T_4 levels before and after stimulation	—	Bovine TSH has been replaced by recombinant human TSH	It can be considered but is prohibitively expensive
Total or free T_3	Protein-bound and free T_3 levels	—	Normal in up to 90% of hypothyroid dogs	No
Reverse T_3	Levels of inactive form of T_3	—	Controlled study validation is missing in dogs	No
Ultrasonography	Thyroid volume and echogenicity	—	Visible differences exist between normal or euthyroid and hypothyroid dogs	Yes, as an adjunct

ence of nonthyroidal illness (Figure 4). The next step would be to run a highly sensitive test (i.e., total T_4 level) for screening and a more specific test (i.e., canine TSH level) to help confirm the diagnosis (Table 2). In some instances, a concurrent illness may not be able to be resolved (e.g., diabetes mellitus, chronic renal failure); because TSH is minimally affected by concurrent disease,[53] it is still recommended to proceed with these tests. The data in Table 2 demonstrate that by using a combination of tests, clinicians can obtain a highly reliable result. However, in some situations, test results are unclear. This occurs with early (subclinical) hypothyroidism, secondary hypothyroidism (sick euthyroid), anti-T_4 antibodies, or other causes of thyroid hormone suppression. In these situations, obtaining a free T_4 level can be a secondary test to help indicate an animal's thyroid status. In some instances, early (subclinical) hypothyroidism or unclear results may be detected; a rational approach would be to retest the animal in 4 weeks.

OTHER FACTORS THAT ALTER THYROID FUNCTION TEST RESULTS

Besides sick euthyroid syndrome, additional factors can alter the results of thyroid function tests, potentially

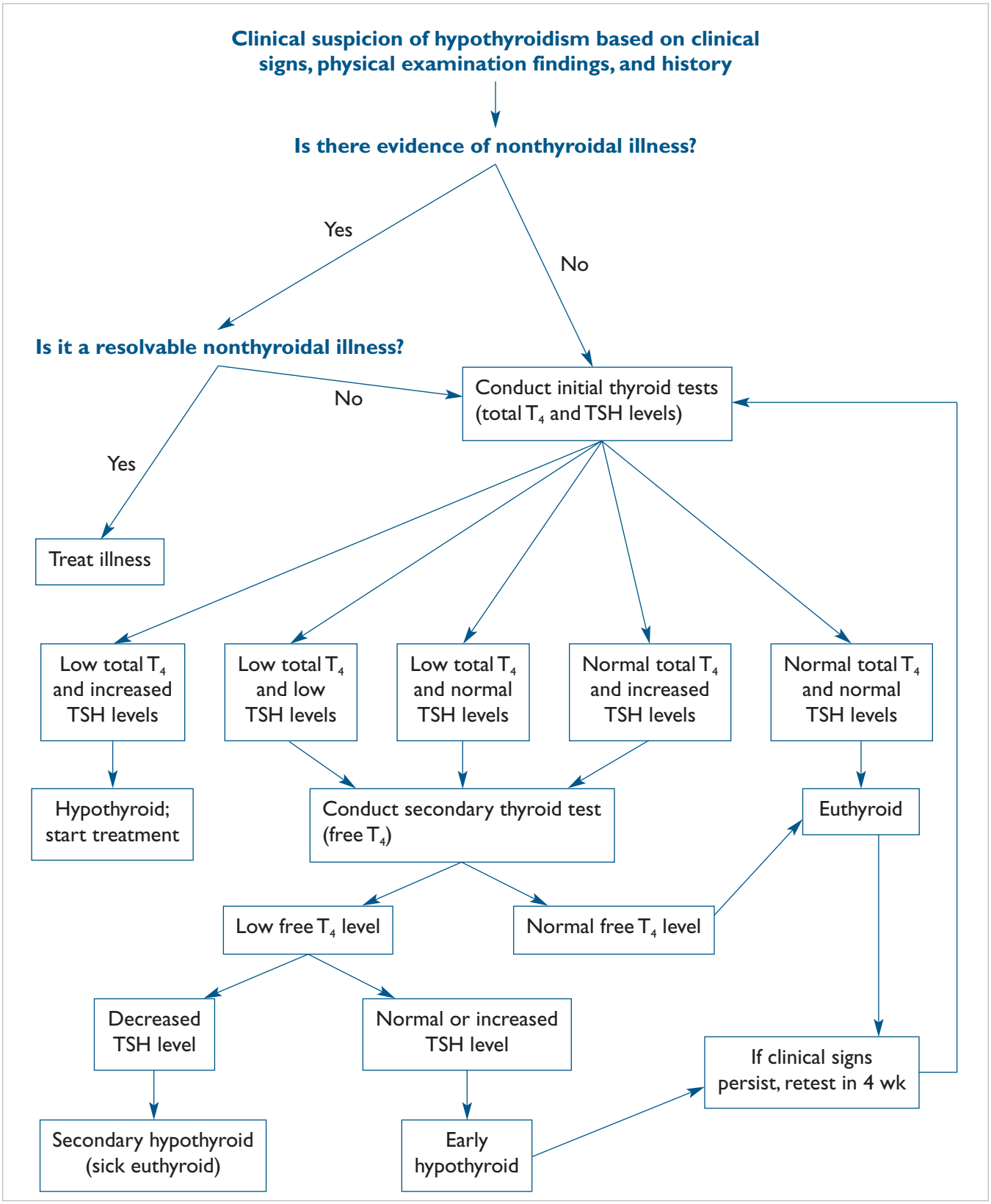


Figure 4. **Diagnosis of hypothyroidism.**

Table 2. Comparison of Canine Thyroid Diagnostic Tests

	Total T_4		Free T_4 (ED)		TSH		Total T_4/TSH		Free T_4 (ED)/TSH	
Study	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Peterson et al[46]	89%	82%	98%	93%	76%	93%	67%	98%	74%	98%
Dixon and Mooney[47]	100%	75.3%	80%	93.5%	86.7%	81.8%	86.7%	92.2%	80%	97.4%

ED = by equilibrium dialysis.

resulting in misdiagnosis (see box on this page). Most reported factors cause an artificial decrease in thyroid hormone levels. Many drugs affect thyroid hormone levels and may result in an animal developing clinical signs of hypothyroidism. The exact mechanisms for each factor are not completely and individually understood. However, decreased binding of thyroid hormone to proteins and the ability of certain drugs to bind iodine, making it less available for thyroid hormone synthesis, are two mechanisms explaining how certain drugs can cause decreased thyroid hormone levels. Sulfonamides,[18,58,59] glucocorticoids,[60,61] phenobarbital,[62,63] clomipramine,[64] and NSAIDs[18,65] have all reportedly decreased circulating thyroid hormone levels in animals. Sulfonamides inhibit thyroid peroxidase and decrease iodine organification and thus production of T_3 and T_4. This effect is noted to occur within weeks of initiation of therapy and disappears 2 weeks after therapy has been discontinued.[59] Glucocorticoids inhibit the entire hypothalamic–pituitary–thyroid axis and have a direct effect against thyroid hormone.[18] The effects of phenobarbital are noted only in animals receiving long-term treatment. To produce reliable results, clinicians should not administer phenobarbital to patients for 4 weeks before thyroid function testing.[18,63] Various studies[18,65] have found the influence of NSAIDs to be variable, depending on the specific agent used. In animals that receive any of these medications, evaluation of thyroid function must be made with caution and preferably after they have stopped receiving the medications well in advance.

Another factor well documented to result in lower thyroid hormone levels is athletic conditioning and training. Several studies[66–70] have demonstrated that well-conditioned sled dogs and greyhounds reliably have lower total and free T_4 levels, which may lead to misdiagnosis of hypothyroidism. In addition, recent vaccination has been demonstrated to cause a transient increase in circulating autoantibody levels. This may cause a truly hypothyroid animal to appear euthyroid and may result in a delay or discontinuation of appropriate therapy. Thyroid function testing should not be conducted if a patient has been vaccinated within the previous 2 weeks.[13]

TREATMENT AND THERAPEUTIC MONITORING

Synthetic thyroid hormone supplementation easily treats hypothyroidism. Levothyroxine sodium is available as both human and veterinary products. It is recommended to avoid generic forms of the drug because human studies have demonstrated wide variability in the bioavailability of generic forms.[2,71] If a generic form is used, it is important to always prescribe the same formulation to an individual patient. Hormone supplementation is usually initiated at 0.02 mg/kg PO q12h. Thyroid function testing is recommended 6 weeks after therapy has begun. The total T_4 level should be monitored and timed so that blood is taken 6 hours after pill administration.[1,72] In stable, well-controlled animals, the total treatment may be given once daily with excellent clinical results, as long as adequate peak hormone concentrations

Factors Affecting Thyroid Function Test Results

Decreased thyroid hormone levels
- Drugs: sulfonamides, glucocorticoids, phenobarbital, clomipramine, NSAIDs
- Good conditioning: racing greyhounds, sled dogs
- Other illness

Increased thyroid hormone levels
- Recent vaccination
- Presence of antithyroglobulin antibodies

are achieved.[42] In animals that receive supplementation once daily, blood should be taken immediately before the medication is given and then again 6 hours later. When therapy is appropriate, the total T_4 level should be high normal to high. If the total T_4 level is significantly above normal, the medication dose should be decreased or the frequency changed. If the total T_4 level is low, an increase in the dose may be necessary. Before increasing the dose, the clinician must assess client compliance, ensure that no gastrointestinal issues will impact absorption, and confirm that there has not been a switch in the levothyroxine formulation. Supplementation levels can be increased to a maximum of 0.8 mg per dog per treatment. It should be noted that levothyroxine doses for dogs exceed those for humans and may confuse pharmacists or endocrinologists.[71] Thyroid function should be monitored every 6 to 8 weeks for the first 6 to 8 months of treatment and then once or twice yearly.[1,72]

Evaluation of TSH is a controversial tool to help assess response to therapy. In a well-controlled animal, the TSH level would be expected to be in the normal range. However, there is a report[72] indicating that the TSH level may be normal in as many as 75% of dogs requiring an increase in their supplementation levels. An increased TSH level is a predictable indicator of the need to increase supplementation levels to achieve adequate hormone control. However, a normal TSH level alone does not indicate that hormone supplementation is adequate in all dogs.[72]

An important aspect to help assess response to therapy is the degree to which clinical signs of hypothyroidism resolve. Marked improvement in the patient's attitude, activity level, and alertness should occur within 1 week of starting therapy. Polyneuropathy usually starts to improve quickly, but complete resolution may take several months.[29] The hematocrit count and serum cholesterol level should gradually resolve in the first weeks of therapy.[72] Dermatologic abnormalities improve slowly, with complete resolution usually taking up to 3 months.[1,72] Response to treatment is a valuable tool to help determine the success of therapy but should not replace appropriate blood tests. Hypothyroidism can be easily and successfully controlled, and the prognosis for affected animals, when appropriately treated, is excellent.

MYXEDEMA COMA

Myxedema coma is a rare, life-threatening, extreme manifestation of severe hypothyroidism and is considered an endocrine emergency. The mortality rate in humans ranges from 15% to 60%.[32,73] Myxedema coma is rare in animals, and much of what is known in veterinary medicine is based on a few case reports[23,74] or is taken from human medicine. The development of myxedema coma requires a precipitating event that overwhelms normal homeostatic mechanisms. In humans, this is often an infection,[32] whereas in animals, no single event has been repeatedly identified.

The common findings in patients with myxedema coma are changes in mental status, altered thermoregulation, and nonpitting skin edema.[8,23,73,74] Mentation changes can range from altered alertness to coma. Coma does not always occur, and in humans, mental depression is the most common assessment of mental status.[32] Edema, localizing in the brain, is responsible for the development of altered mentation. Hyponatremia can cause a further decrease in the neurologic status.[32] Patients with myxedema coma are often hypothermic but not shivering. Thyroid hormone has a permissive effect on calcium ATPase. In the hypothyroid state, there is decreased activity of this enzyme, resulting in decreased ATP use.[73] ATP is the powerhouse of the cell, and with decreased activity, there is decreased oxygen consumption and thus decreased heat generation. In addition, hypothalamic dysfunction, secondary to edema formation in the brain, may lead to alteration in the thermoregulatory set-point.[32,73] These changes may result in a lower body temperature and reduced likelihood to shiver. Shivering can be stimulated by the hypothalamus or sympathetic nervous system. T_4 amplifies catecholamine function, helping to stimulate muscular activity associated with shivering[74]; therefore, a reduced T_4 level blunts the ability to shiver. Hypothermia reduces platelet function, resulting in hepatic platelet sequestration and decreased enzymatic activity within the coagu-

Myxedema coma is a manifestation of severe hypothyroidism. Affected animals have altered mentation, are hypothermic without shivering, and have nonpitting edema.

lation cascade.[74] With a decreased body temperature, there is peripheral vasoconstriction and central shunting of blood. Nonpitting edema of the skin is due to deposition of glycosaminoglycans in the interstitial space.[1,73]

Initial laboratory tests reveal hypercholesterolemia, hypertriglyceridemia, hypoglycemia, anemia, hyponatremia, hypoxemia, and hypercarbia.[73,74] Thyroid function tests indicate severe hypothyroidism with low total T_4, low free T_4, and elevated TSH levels.[74] After a diagnosis of myxedema coma has been made, immediate treatment is necessary (see box on this page). This usually means initiating treatment before thyroid function test results confirm clinical suspicion of myxedema coma. Initial attention must be paid to the provision of a patent airway and resuscitation of hypotension. Mechanical ventilation, which has been described in humans and dogs, may be necessary.[33,73] The goals of fluid therapy are to support blood pressure and to address decreased sodium levels. Clinicians must remember that patients with myxedema coma have a decreased ability to clear free water. The hallmark of therapy is intravenous administration of synthetic thyroid hormone. A levothyroxine dose of 5 µg/kg IV q12h is most commonly described.[1,2,73] A more conservative replacement dose should be used when there is concern about cardiac function, especially the heart's ability to deal with a sudden and rapid increase in the metabolic rate.[73,74] Rapid rewarming of patients with myxedema coma must be avoided because this may result in peripheral vasodilation, hypotension, and potential cardiovascular collapse. Correction of hypothermia should be passive and should occur over a number of hours.

The greatest challenge in treating myxedema coma is recognizing the syndrome. Once it is recognized, immediate and intensive supportive care is necessary to treat the patient. Successful treatment has been reported in dogs and humans[33,74]; however, mortality rates can be high.[32]

Treating Myxedema Coma

- Establish an airway.
- Ensure adequate ventilation.
- Administer intravenous fluids: 0.9% sodium chloride (20 ml/kg [initial bolus]). Reassess and continue intravenous fluids (2.5–7 ml/kg/hr). Select rate based on blood pressure, heart rhythm, heart rate, and respiratory rate.
- Administer levothyroxine at 5 µg/kg (0.005 mg/kg) IV q12h.[a]
- Once the animal can swallow, start levothyroxine at 20 µg/kg (0.02 mg/kg) PO q12h. This dose can be started while still using intravenous levothyroxine to help achieve therapeutic blood levels.[a]
- Use passive rewarming (via water blankets or forced-air devices). Continue until the temperature is low normal and can be maintained without support.

[a]The levothyroxine dose should be decreased by 50%–75% if there is preexisting heart disease.[73]

CONCLUSION

Hypothyroidism is a common endocrine disease in dogs but is rare in cats. The most common forms of hypothyroidism are lymphocytic thyroiditis and idiopathic thyroid atrophy. The clinical signs of the disease are vague and can affect many body systems. Evaluation of the total T_4 level is considered an excellent screening test. Evaluation of the canine TSH level is a good confirmatory test and has a specificity of 98% when it is used in conjunction with evaluation of the total or free T_4 levels. Several factors may alter the results of thyroid function testing. The presence of anti-T_4 antibodies can falsely increase total T_4 levels and mask true hypothyroidism. Alternatively, many drugs and athletic conditioning, in some breeds, may decrease total T_4 levels while not being associated with a true hypothyroid state. Treatment of hypothyroidism is easily achieved with levothyroxine supplementation. Success of therapy must be assessed with close monitoring via thyroid function testing. With appropriate treatment, hypothyroidism can be well managed and have an excellent prognosis. A rare complication of severe hypothyroidism is myxedema coma. This condition is difficult to recognize but is associated with an altered mental state, hypothermia without shivering, and nonpitting skin edema. With aggressive supportive therapy and intravenous thyroid hormone replacement, this condition may be successfully treated, although the mortality rate remains high.

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ARTICLE #1 CE TEST

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1. Which organ/gland is not directly involved in thyroid hormone production and regulation?

a. thyroid
b. hypothalamus
c. adrenal gland
d. pituitary

2. Which stimulatory hormone is produced in the pituitary?

a. TSH
b. TRH
c. T_4
d. T_3

3. How much of the total T_4 is free (i.e., unbound to protein)?

a. 0%
b. <1%
c. 10%
d. 99%

4. Which are the major forms of acquired hypothyroidism in dogs and humans?

a. neoplastic destruction of the thyroid and idiopathic thyroid atrophy
b. radioiodine treatment and infection of the thyroid
c. idiopathic thyroid atrophy and lymphocytic thyroiditis
d. idiopathic thyroid atrophy and iodine deficiency

5. Which panel gives clinicians the most initial information to assess thyroid function?

a. total T_4 and TSH
b. total T_3
c. total T_3, reverse T_3, and free T_4
d. total T_4 and antithyroglobulin antibodies

6. Which interpretation of the following thyroid function profile is correct?

Total T_4 level	TSH level	Free T_4 level
Decreased	Decreased	Decreased

a. euthyroid
b. unclear; retest the patient in 4 weeks
c. hypothyroid
d. secondary hypothyroidism (sick euthyroid)

7. A dog has been receiving levothyroxine supplementation at a dosage of 0.02 mg/kg PO q12h for 6 weeks. The thyroid function test results follow. (Blood was taken 6 hours after pill administration.)

Total T_4 level	TSH level
High normal	Normal

What should be the next treatment step?

a. Continue with the same treatment, and retest the patient in 6 to 8 weeks.
b. Decrease the levothyroxine dose to every 24 hours.
c. Increase the levothyroxine dose.
d. The dog is not hypothyroid. Stop all treatment.

8. Resolution of clinical signs is helpful in assessing response to therapy. Which typical clinical sign of hypothyroidism can take many months to completely resolve?

a. weakness
b. anemia
c. dermatologic abnormalities
d. lethargy

9. Which is not an immediate treatment of myxedema coma in dogs?

a. intravenous levothyroxine administration
b. airway establishment
c. intravenous fluid therapy with 0.9% sodium chloride
d. rapid resuscitation of hypothermia

10. Which is not a common clinical sign or laboratory finding of myxedema coma?

a. hyponatremia
b. altered mental status
c. nonpitting edema of the skin
d. tachycardia