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Original Study

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Evaluation of serum thyroid hormones in dogs with systemic inflammatory response syndrome or sepsis

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Abstract

Objective – To determine whether dogs with systemic inflammatory response syndrome (SIRS) or sepsis have derangements in serum thyroid hormone concentrations and to evaluate whether such derangements relate to illness severity or outcome.
Design – Prospective observational study. Dogs hospitalized with SIRS or sepsis between May and December 2010 were included. Serum thyroid hormone concentrations were measured in all dogs. Data obtained on admission were used to calculate the Acute Patient Physiologic and Laboratory Evaluation (APPLE) scores.
Setting – University teaching hospital.
Animals – Twenty-two consecutive client-owned dogs hospitalized with SIRS or sepsis were enrolled; 18 dogs completed the study and 4 dogs were excluded for incomplete data. Forty-nine healthy dogs owned by volunteers were used as controls.
Interventions – None.
Measurements and Main Results – Decreased total thyroxine (TT4) concentrations were documented in all septic and 7/9 dogs with SIRS. Free T4 concentrations were decreased, but were within the reference interval in 12/18 dogs with SIRS or sepsis compared to control dogs ($P < 0.001$). Dogs with increased APPLE(fast) scores were less likely to survive ($P = 0.017$).
Conclusions – Dogs with SIRS or sepsis have derangements in measured serum thyroid hormones. No relationships were identified between thyroid hormone concentrations and survival. The APPLE(fast) score was the only variable predictive of poor outcome.

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Keywords: APPLE score, critical illness, endocrine function, illness severity, SIRS

The hypothalamic-hypophyseal-thyroid (HHT) axis is composed of the interactions between the hypothalamus, anterior pituitary, and thyroid gland that result in the secretion of thyroid hormones. In the dog, the majority of circulating thyroxine (T4) and 20% of the biologically active tri-iodothyronine (T3) are produced by the thyroid gland in response to thyroid-stimulating hormone (TSH) secreted by the pituitary gland. Both T4 and T3 are tightly bound to thyroid-binding globulin

Abbreviations

APPLE	Acute Patient Physiologic and Laboratory Evaluation
fT4	free thyroxine
HHT	hypothalamic-hypophyseal-thyroid
IQR	interquartile range
NTI	nonthyroidal illness
ROC	receiver operator curve
SIRS	systemic inflammatory response syndrome
TBG	thyroid-binding globulin
TSH	thyroid-stimulating hormone
TT4	total thyroxine
T3	tri-iodothyronine

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(TBG) in the blood stream. However, only free thyroid hormone (fT4) is able to enter cells and produce a biological effect. Thyroid hormones affect virtually every cell in the body, are responsible for normal metabolism, growth, and maintenance of the cardiovascular, reproductive, and CNSs. In the absence of adequate amounts of thyroid hormones or the ability for cells to utilize them, the homeostasis of multiple organ systems may become deranged.[1]

In health, thyroid hormone homeostasis is regulated by negative feedback loops from the thyroid to the pituitary and hypothalamus.[1] In patients with critical illness, changes in thyroid hormone concentrations arise in the absence of an intrinsic abnormality in thyroid function, comprising the syndrome of nonthyroidal illness (NTI).[2] The derangement in thyroid hormone homeostasis is multifactorial and attributed to reduced binding of thyroid hormones to TBG, reduced TSH production, changes in thyroid hormone receptor expression, and reduced peripheral deiodination.[1,3] Factors contributing to NTI in patients with sepsis, trauma, or autoimmune disease include the production of inflammatory cytokines and reactive oxygen species, which have been shown to suppress TSH release.[2,4] Malnutrition and the administration of glucocorticoids and dopaminergic drugs may further impair TSH production.[2]

Derangements of the HHT axis occur commonly in critically ill people.[5,6] Plasma T3 concentrations decrease within hours of trauma or surgery and the magnitude of this change is related to the severity of disease.[6,7] As the acute insult progresses in duration or severity, circulating T4 and TSH concentrations also decline. Low serum concentrations of T4 and TSH in human patients with critical illness are associated with a decreased survival in adults, neonates undergoing open heart surgery, and children with sepsis and septic shock.[8–10]

NTI is characterized in dogs by decreased serum total thyroxine (TT4) and free thyroxine (fT4) concentrations with a decreased to normal serum TSH concentration.[1] Several studies have evaluated the prevalence of NTI in critically ill dogs.[11–13] Decreased serum concentrations of T4, T3, and fT4 were reported in dogs with a variety of NTI of differing severity, while TSH concentrations remained within the reference interval. Serial thyroid hormone measurements obtained from puppies with parvoviral enteritis found a decrease in serum T4 and fT4 concentrations, which was associated with a lower likelihood of survival.[13]

An objective assessment of illness severity in dogs with NTI has not been previously performed. Recently, a new objective illness severity score, (ie, Acute Patient Physiologic and Laboratory Evaluation health evaluation score [APPLE]) has been developed for dogs based on physiologic and biochemical variables obtained at the time of hospital admission. This score remains to be validated in clinical populations.[14]

Table 1: Inclusion criteria for canine SIRS or sepsis[15]

SIRS: ≥ 2 of the following criteria **Sepsis: SIRS with confirmed source of infection**	
Tachycardia (heart rate/min)	>140
Tachypnea (respiratory rate/min)	>20
WBC count ($\times 10^9$ /L)	<6.0 or >16.0
Immature (band) neutrophils	>3%
Temperature (°C)	<37.8 or >39.4

The goals of this study were to determine the prevalence of NTI in dogs with systemic inflammatory response syndrome (SIRS) or sepsis and to determine an association between thyroid hormone concentration and illness severity as determined by use of the APPLE score. We hypothesized that dogs with SIRS or sepsis would have NTI characterized by decreased serum TT4, fT4, and TSH concentrations compared to control dogs. Serum thyroid hormones and APPLE scores were also evaluated as predictors of mortality.

Materials and Methods

This was an observational, prospective study of dogs older than 6 months of age, admitted to a university teaching hospital's small animal ICU that met SIRS criteria (Table 1) between May and December of 2010.[15] Dogs weighing at least 10 kg were deemed eligible based on ability to tolerate 11 mL of blood removed. Twenty-two dogs admitted were enrolled. Eleven dogs were categorized as having noninfectious SIRS (SIRS group). A source of infection in these dogs was not identified via cytology or bacterial culture as determined by the primary clinician. Another 11 dogs were determined to have sepsis (Sepsis group) by fulfilling SIRS criteria and having evidence of infection based on cytology or bacterial culture. Parvoviral enteritis was diagnosed by a bedside ELISA fecal antigen test.[a] Rickettsial disease antibody titers were obtained on all patients suspected of having rickettsial disease. The primary clinician determined all treatment regimens and there were no interventions as part of the study.

Additionally, 49 clinically healthy dogs were recruited among the staff of the university teaching hospital. These dogs were selected based on a normal physical examination, absence of known endocrine disease, and ability to tolerate having 11 mL of blood removed.

This study protocol was approved by the College of Veterinary Medicine and Biomedical Sciences, Texas

A&M University's Clinical Review Research Committee, and informed consent was obtained from the owners of all dogs in the study. A predetermined amount of funding limited the total number of dogs eligible for the study.

The study dogs had blood drawn serially as part of a concurrent study on biomarkers in dogs with critical illness. For the purposes of this study, serum concentrations of TT4, fT4 (by equilibrium dialysis), TSH, and a serum biochemistry profile were measured once within 12 hours of admission. In addition, the patients had blood drawn every 6 hours for PCV, total plasma protein, glucose, and an estimation of BUN on a colorimetric strip for routine ICU monitoring.

The APPLE score was calculated according to a previous report.[14] The APPLE(full) score was calculated using serum creatinine, WBC count, serum albumin, SpO_2, serum total bilirubin, mentation, respiratory rate, age, fluid score, and plasma lactate (Table 2). The APPLE(fast) score was calculated using blood glucose, serum albumin, plasma lactate, platelet count, and mentation score (Table 3). Mentation status and fluid scores were calculated according to the values described in Table 4. All scores were calculated with data obtained upon presentation. The medical records of all patients were reviewed for descriptive data consisting of age, breed, reproductive status, disease, length of hospital stay, cost of hospitalization, and outcome.

Sample handling

Eleven milliliters of blood was drawn from a central IV catheter in the hospitalized patients or via venipuncture in the control dogs. Approximately 9 mL of blood was placed in 3 separate lithium heparin tubes and 1 plain tube with no additive. One lithium heparin tube was submitted for a biochemistry profile. After a firm clot had formed, the plain tube was centrifuged at 197 $\times$ *g* for 10 minutes to separate the serum from the red cell mass. The serum was decanted and frozen at -80°C for batched thyroid hormone measurement.

Thyroid hormone measurement

Total T4 was measured using an automated chemiluminescent competitive immunoassay.[b] TSH was measured using an automated solid-phase, enzyme-labeled chemiluminescent immunometric assay.[c] Free T4 was measured by equilibrium dialysis radioimmunoassay.[d] All assays were performed according to the manufacturer's instructions. For statistical analysis, results measuring below the lower detection limit of an assay were assigned the lowest measurable value.

Statistical Methods

All data were evaluated for normal distribution using both a Kolmogorov–Smirnov and Shapiro–Wilk test for normality. Age, TT4, and TSH concentrations were compared between healthy dogs, dogs with SIRS, and dogs with sepsis using a Kruskal–Wallis test. Significant data was then further compared using a Dunn's multiple comparison post test. Mean fT4 concentrations were compared among groups using a one-way ANOVA and Tukey's multiple comparison post test. Concentrations of fT4, TT4, and TSH as well as both APPLE full and fast scores were compared between survivors and nonsurvivors using a Mann–Whitney *t*-test as data was not normally distributed.

To determine how the APPLE full and fast scores predicted mortality as a diagnostic test, a receiver operator curve (ROC) and the area under the ROC were calculated. Sensitivity and specificity were determined for both APPLE scores at previously published cut-off suggestions.[14]

Since the number of dogs that entered the study was limited by study funds, a post-hoc power analysis was performed after completion of the study. Alpha was set at 0.05 for all statistical analyses. All analyses were performed with a commercially available statistical software package.[e]

Results

A total of 22 dogs with SIRS (11 dogs) or sepsis (11 dogs) were enrolled into the study. Four dogs (2 from each group) were excluded due to incomplete data. The final 18 dogs represented the following breeds: German Shepherd (2), Labrador Retriever (2), Boxer (2), Rottweiler (2), Brittany Spaniel (2), and 1 each of Australian Kelpi, Border Collie, Collie, Dogo Argentino, Great Dane, Old English Sheepdog, Weimeraner, and a mixed breed. The median age of dogs with SIRS was 5 years (range 1–13 years). The median age of dogs with sepsis was 3 years (range 0.5–8 years). The healthy control group of dogs ($n = 49$) was made up of a diverse group of breeds. The median age of control dogs was 5 years (range 1–13 years). The Kruskal–Wallis test showed no significant difference in the ages between the 3 groups of dogs ($P = 0.12$).

Within the SIRS group, 3 dogs were diagnosed with a gastrointestinal foreign body/obstruction, and 1 dog each with mast cell tumor and pancreatitis, soft tissue trauma, pancreatic adenocarcinoma, lymphoma, gastrointestinal ulceration, and immune-mediated hemolytic anemia. Within the sepsis group, 4 dogs were diagnosed with septic peritonitis, 2 with parvoviral enteritis, and 1 dog each with pyelonephritis,

Table 2: APPLE (full) score. Calculated by adding the values in the upper left corner of each cell for the 10 parameters listed, with a maximum score of 80[14]

			Creatinine (μmol/L)	**1**	**8**	**9**	
			0–55	56–120	121–200	>200	
		9	WBC (×10^9/L)	**2**	**3**		
		<5.1	5.1–8.5	8.6–18	>18		
6	**7**	**9**	Albumin (g/L)	**2**			
<26	26–30	31–32	33–35	>35			
10	**4**	**1**	SpO_2 (%)				
<90	90–94	95–97	98–100				
			Total bilirubin (μmol/L)	**6**	**4**	**3**	
			0–4	5–8	9–16	>16	
			Mentation score	**5**	**7**	**8**	**13**
			0	1	2	3	4
			Respiratory rate (per min)	**3**	**5**	**6**	**5**
			<25	25–36	37–48	49–60	>60
			Age (years)	**6**	**8**	**7**	
			0–2	3–5	6–8	>8	
	3	**4**	Fluid score				
	2	1	0				
			Lactate (mmol/L)	**2**	**3**	**6**	
			0—1.9	2.0–7.9	8.0–11.0	>11	

Table 3: APPLE (fast) score. Calculated by adding the values in the upper left corner of each cell for the 5 parameters listed, with a maximum score of 50[14]

7	**8**	**9**	**10**	Glucose (mmol/L)			
<4.6	4.6–5.6	5.7–9.0	9.1–15.0	>15.0			
	8	**7**	**6**	Albumin (g/L)			
	<26	26–30	31–32	33–35			
				Lactate (mmol/L)	**4**	**8**	**12**
				<2	2–8	8–10	>10
	5	**6**	**3**	Platelet count	**1**		
	<151	151–200	201–260	261–420,000	>420		
				Mentation score	**4**	**6**	**7**	**14**
				0	1	2	3	4

Table 4: Body cavity fluid score and mentation score calculation.[14] FAST, Focused Assessment Sonography for Trauma; TFAST, Thoracic Focused Assessment Sonography for Trauma

Mentation score: Assessed at Admission before sedation/analgesic administration	Fluid score (Ultrasonographic evaluation, as assessed by FAST or TFAST technique)
0. Normal	0. No abdominal, thoracic, or pericardial free fluid identified
1. Able to stand unassisted, responsive but dull	1. Abdominal OR thoracic OR pericardial free fluid identified
2. Can stand only when assisted, responsive but dull	2. Two or more of abdominal, thoracic, and pericardial free fluid identified
3. Unable to stand, responsive	
4. Unable to stand, unresponsive	

body wall abscess, and Rocky Mountain Spotted Fever. In total, 6 dogs (3 SIRS and 3 septic dogs) died or were euthanized during the study.

The results of TT4, TSH, and fT4 testing for dogs with both sepsis and SIRS are described in Table 5. There was a significant difference in serum TT4 ($P < 0.001$) and TSH ($P = 0.019$) concentrations among the 3 groups. Post testing revealed that the serum TT4 concentration of the control group (median = 2.55 μg/dL, interquartile range (IQR): 1.81 to 3.24) was significantly greater than that of the SIRS group (median = 0.50 μg/dL, IQR: 0.50–1.70; $P < 0.05$) and the sepsis group (median = 0.50 μg/dL, IQR: 0.50–0.87; $P < 0.05$; Figure 1). Additionally, the post test demonstrated that the serum TSH concentration of the control group (median = 0.12 ng/mL; IQR: 0.09 to 0.21) was significantly greater than the SIRS group (median = 0.04 ng/mL; IQR: 0.03 to 0.11; $P < 0.05$) but not the sepsis group (median = 0.08 ng/mL; IQR: 0.03 to 0.18; $P > 0.05$). There was no difference in the serum TSH concentration between the SIRS and the sepsis groups (Figure 2). Free T4 concentrations were also significantly different between groups ($P < 0.001$). The post test showed that the serum

Table 5: Results of thyroid function testing in dogs with sepsis or SIRS. RI, reference interval

	TT4 (1.61 - 3.6 μg/dL)			Free T4 (0.6–3.7 ng/dL)			TSH (0–0.32 ng/mL)		
	# Below RI	# in RI	# Above RI	# Below RI	# in RI	# Above RI	# Below RI	# in RI	# Above RI
Sepsis	9	0	0	1	7	1	n/a	8	1
SIRS	7	1	1	4	5	0	n/a	8	1

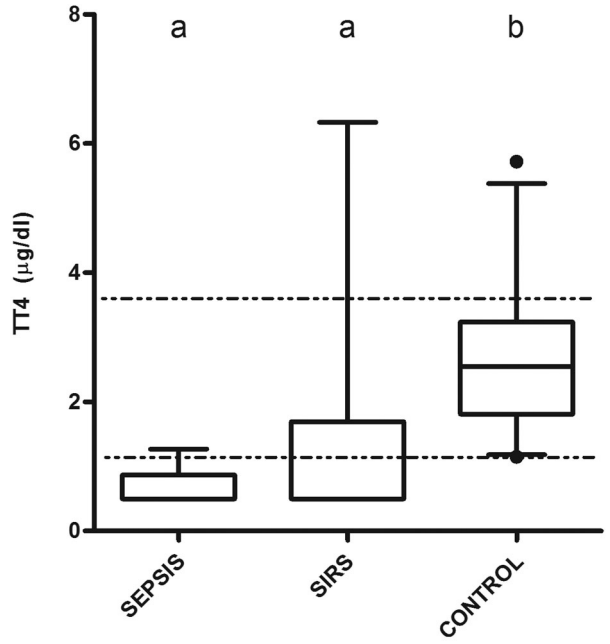

Figure 1: Comparison of serum total T4 concentrations between dogs with sepsis, dogs with SIRS, and healthy control dogs. The whiskers of the plot represent the 2.5 and 97.5 percentile. The dashed line indicates the reference interval (1.61–3.6 μg/dL). Groups assigned different lower-case letters are statistically different. Groups assigned the same letter are not statistically different.

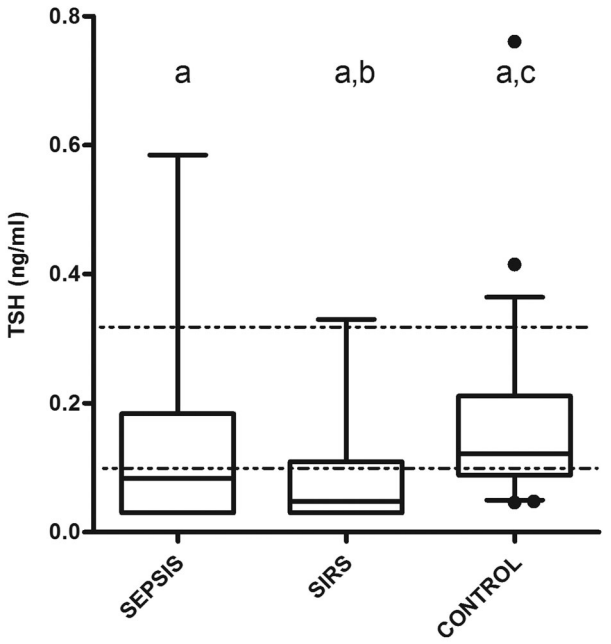

Figure 2: Comparison of serum TSH concentrations between dogs with sepsis, dogs with SIRS, and healthy control dogs. The whiskers of the plot represent the 2.5 and 97.5 percentile. The dashed line indicates the reference interval (0–0.32 ng/mL). Groups assigned different lower-case letters are statistically different. Groups assigned the same letter are not statistically different.

fT4 concentration of the control group (mean = 2.36 ng/dL, SD: 0.67) was significantly greater than both the SIRS group (mean = 1.31 ng/dL, SD: 1.16; $P < 0.05$) and the sepsis group (mean = 1.49 ng/dL; SD: 1.07; $P < 0.05$; Figure 3).

Both SIRS and sepsis dogs were combined, then separated based on survival or nonsurvival and compared based on their serum TT4, fT4, and TSH concentrations and APPLE(full) and APPLE(fast) scores. A Mann-Whitney test demonstrated a significant difference in only the APPLE(fast) score between the 2 groups ($P = 0.017$; Figure 4). Dogs that lived had a median APPLE(fast) score of 22, (IQR: 19.00 to 27.25), while dogs that died had a median APPLE(fast) score of 29.5 (IQR: 25.50 to 36.00). The APPLE(full) score approached significance ($P = 0.054$). The correlation between APPLE(full) and APPLE(fast) scores was $r = 0.7$ ($P = 0.0012$) for our dataset. The other comparisons between survivor and nonsurvivor groups demonstrated nonsignificant P values for serum TT4 ($P = 0.43$), fT4 ($P = 0.19$), or TSH ($P = 0.36$) concentrations. Post hoc analysis demonstrated that the study was not sufficiently powered to detect a 10% survival difference in thyroid hormone concentrations or APPLE scores.

The area under the ROC for the APPLE(full) and the APPLE(fast) score was 0.79 and 0.86, respectively, for its use as a diagnostic test to predict mortality. The APPLE(full) and APPLE(fast) scores were compared to the original score's cut-offs for specificity and sensitivity for predicting mortality.[14] At an APPLE(full) score of 30 the sensitivity was 83.3% and the specificity was 41.7%. An APPLE(full) score of 40 had a sensitivity of 50.0% while

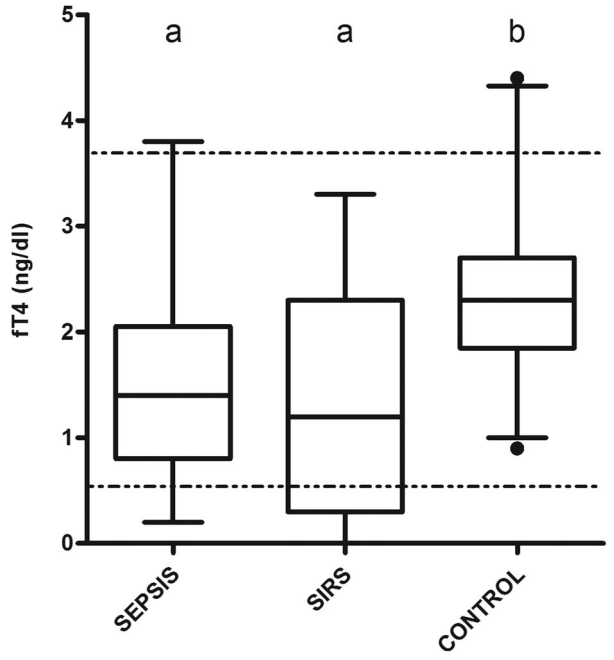

Figure 3: Comparison of serum fT4 concentrations between dogs with sepsis, dogs with SIRS, and healthy control dogs. The whiskers of the plot represent the 2.5 and 97.5 percentile. The dashed line indicates the reference interval (0.6–3.7 ng/dL). Groups assigned different lower-case letters are statistically different. Groups assigned the same letter are not statistically different.

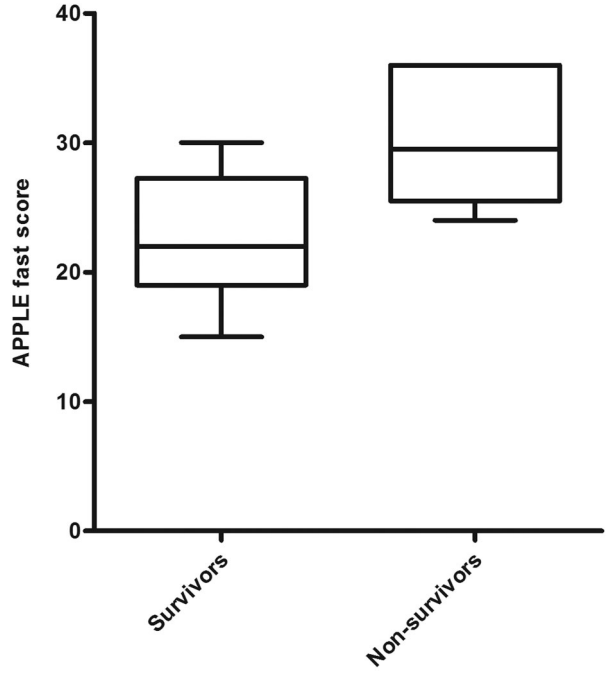

Figure 4: Comparison of APPLE(fast) scores between survivors and nonsurvivors. The whiskers of the plot represent the 2.5 and 97.5 percentile.

the specificity was 83.3%. At an APPLE(fast) score of 22, the sensitivity was 100.0% and the specificity was 50.0%. Finally, an APPLE(fast) score of 25 yielded a sensitivity of 83.3% and a specificity of 66.7%.

Discussion

The results showed significant differences in serum thyroid hormone concentrations between control dogs and study dogs, confirming our hypothesis. Median TT4 concentrations in both SIRS and sepsis dogs were below the reference interval, which was in agreement with previous studies showing a decrease in serum TT4 in critically ill dogs.[11–13,16] Median fT4 concentrations in dogs with SIRS or sepsis were decreased compared to control dogs, but were still in the reference interval. TSH concentrations were significantly lower in dogs with SIRS compared to controls, but were not significantly different between the SIRS and the sepsis group.

In this patient population, the APPLE(fast) score was the only variable associated with nonsurvival, whereas the APPLE(full) score did not show association with nonsurvival. The 2 scores evaluate different patient variables, with the APPLE(fast) score including glucose and platelet counts and excluding physical and bloodwork parameters included in the APPLE(full) score. It is possible that the significance of hypoglycemia or thrombocytopenia outweighs the significance of the variables included in the APPLE(full) score and further clinical validation of the APPLE scores could expand on this finding.

A notable result of our study was the substantial decrease in TT4 of study dogs, while fT4 decreased but remained within the reference interval in the majority of study dogs. TT4 is tightly bound to TBG in circulation, however, TBG is a negative acute phase protein and may decrease in acute critical illness. This is likely to account for part of the decrease of TT4 measured in circulation. Other explanations for this finding could include the production of a desialylated form of TBG, which has been demonstrated in human patients with chronic critical illness. This protein has a much lower affinity for thyroid hormones and further increases the fT4 to TT4 ratio.[2] Proteolytic cleavage of TBG and displacement of T4 from TBG in the presence of increased circulating fatty acids or the use of certain drugs (heparin, glucocorticoids, and dopamine) have also been demonstrated in people with sepsis.[8,17] Quantifying serum TBG may be a way to discern whether a reduction in TBG or a change in its biological behavior is responsible for the measured decrease in TT4. Notably, the amount of unbound thyroid hormone remained within the reference interval in the majority of study dogs, suggesting that the biologic

availability of fT4 for maintenance of homeostatic functions was sufficient in those patients.

While the available veterinary literature does not offer a strict definition for NTI, results of our and previous studies evaluating critically ill dogs found a consistent decrease in serum TT4 concentrations.[11,13,18,19] However, changes in serum fT4, TSH, and T3 concentrations appear more unpredictable.[11,13,18,19] The decrease in circulating thyroid hormones in people with NTI has been postulated as an adaptive mechanism in patients with critical illness to conserve energy by decreasing cellular metabolism, oxygen consumption, and maintaining lipid storage.[6] It is reasonable to question if supplementation of thyroid hormones in critically ill dogs with NTI may be of benefit. This issue remains controversial in human medicine and the few studies designed to assess the benefits of thyroid hormone replacement have offered divergent results.[2] There is some indication that supplementation of T3 may be beneficial in human patients undergoing heart transplants or stabilization from heart failure.[20] However, if the NTI state is one of adaptive conservation of energy, supplementing thyroid hormones may have detrimental consequences, such as an increase in metabolic or oxygen demands.[6,8] More prospective randomized studies on naturally occurring NTI in dogs are required before recommendations for supplementation can be made.

In our study, dogs with noninfectious SIRS had the same likelihood of survival as dogs with sepsis (67% for both groups). Recent literature reports survival rates approaching 70% for dogs and cats with sepsis, consistent with the findings of our study.[21–23] Less is known about mortality associated with SIRS. Recently, a single study evaluating survival of dogs with SIRS and sepsis reported a survival rate of 69% in those patients with noninfectious SIRS, compared to 58% in those with sepsis.[24] The synergism between inflammatory signals even in the absence of infection may lead to organ dysfunction and death in a similar fashion to sepsis.[25] Therefore, although extensive information regarding mortality in dogs with SIRS is lacking in the literature, dogs that meet SIRS criteria secondary to a variety of inflammatory, neoplastic, or traumatic causes may be at higher risk of death than dogs that do not.

There were several important limitations to our study. Our patient population lacked homogeneity relative to the small sample size. The variability of illnesses confounded the issue of acute critical illness (perforated bowel for example) versus a more chronic critical illness (such as a decompensated cancer patient). The difference between the 2 has been shown to exhibit significant variability in endocrine derangements in human patients, particularly with respect to thyroid function tests. The variability in nutritional status and nutritional support likely also influenced the severity of NTI in our patients. Furthermore, the study did not control for the administration of medications that could have influenced thyroid hormones (eg, glucocorticoids, heparin, dopamine). In addition, our study was underpowered as suggested by a post hoc power analysis, possibly limiting our ability to find significant associations with outcome. However, there is controversy in the validity of calculating post hoc power analysis.

The lack of a relationship between derangements in thyroid hormone regulation and outcome in our study is in contrast to previous studies that have found associations between thyroid hormone derangements and mortality.[9,12,13,16,26,27] Since association does not imply causality, it is difficult to determine if the thyroid hormone derangements were the cause of mortality or a marker of more severe disease in these studies. The concurrent disease processes in our patients likely had variable effects on the HHT axis; specifically, malnutrition results in decreased release of TRH from the hypothalamus while cytokines result in decreased release of TSH from the pituitary. Intracellular deiodination depends on the health of the particular organ systems (eg, liver, lungs, kidneys), which are often dysfunctional in the patient with SIRS or sepsis. These alterations in homeostasis are presumed to have existed in our patient population, but were not specifically documented. Lastly, it is known that the analytical methods employed in thyroid hormone testing may affect measured concentrations. Free hormone concentrations are often underestimated by current tests and more specific assays for TSH are currently used in human medicine.[2]

In summary, this study demonstrated derangements of the HHT axis in dogs with critical illness. TT4 concentrations decreased in most dogs with SIRS or sepsis, while fT4 concentrations decreased, but remained within the reference interval in the majority of dogs. No associations were identified between any of the measured serum thyroid hormone concentrations and outcome. Dogs with SIRS had the same likelihood of survival as dogs with sepsis. The APPLE(fast) score was the only variable associated with nonsurvival.

Acknowledgment

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Footnotes

[a] SNAP Parvovirus fecal antigen ELISA, IDEXX Laboratories, Westbrook, ME.
[b] Immulite 2000 Canine Total T4, Siemens Healthcare Diagnostics Products Ltd., Deerfield, IL.
[c] Immulite 2000 Canine TSH, Siemens Healthcare Diagnostics Products Ltd.

[d] Free T4 by Equilibrium Dialysis, Nichols Institute Diagnostics, San Clemente, CA.
[e] GraphPad Prism 5, La Jolla, CA.

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