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CASE REPORT
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Minimum Dose of Levothyroxine Restored the Autonomic Balance on a Dalmatian Female Dog with Primary Hypothyroidism

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ABSTRACT

***Background*:** Hypothyroidism is an endocrine disease that leads to a reduction in the hormones thyroxine (T_3) and triiodothyronine (T_4), which therapy with levothyroxine restores the clinical signs related to the metabolic rate. Due to the influence of thyroid hormones on the heart, which is under the constant influence of the autonomic nervous system (ANS), dogs with hypothyroidism can develop bradycardia, arrhythmia, and dysautonomia. Heart rate variability (HRV) assesses autonomic modulation by the Holter method, which is scarce in dogs. We aimed to report the cardiac and autonomic effects of the primary hypothyroidism untreated and treated with levothyroxine in a canine case by Holter monitoring.

***Case*:** A 7-year-old female Dalmatian, weighing 36 kg, was referred for clinical evaluation due to apathy, weight gain, low hair quality, and lethargy. On physical examination, alopecic lesions on the hind limbs and tail, as well as bradycardia with a heart rate (HR) of 40-50 beats per minute (bpm) were observed, in addition to a 3/6 mitral murmur and 2/6 tricuspid murmur. Given the suspicion of thyroid gland disorder, the blood hormonal measurement revealed an increase in thyroid-stimulating hormone (TSH; 0.65 ng/mL) and a decrease in free T_4 (0.11 ng/mL) and total T_4 (0.44 ng/mL), confirming primary hypothyroidism. Therapy was started with a minimum dose of levothyroxine (0.913 mg, every 12 h), which clinical signs were restored in 5 months of treatment, with weight loss, hair growth, and active behavior. To assess the impact of untreated and treated hypothyroidism on the patient's ANS, a Holter monitoring exam was performed for 24 h before and after therapy. Before treatment, the average HR was 75 bpm, and the HR<50 bpm occurred during 05 h 20 min 36 s. Still, 320 pause events (>2.0s), 1st-degree atrioventricular blocks (AVB), six ventricular ectopias events, and 2nd-degree sinoatrial block (SAB) were also observed. The ANS parasympathetic tone was significantly stimulated, highlighting bradycardia, arrhythmia, and dysautonomia. After 5 months of treatment with levothyroxine, the average HR was 89 bpm, and the HR<50 bpm occurred during 02 h 06 min 13 s. No ventricular pauses, blocks, or ectopias were observed, showing the stimulation of sympathetic tonus, which restored HR and ANS balance. Still, it was observed that the minimum levothyroxine dose corrected cardiac changes by increasing the low frequency (LF), decreasing the high frequency (HF), and, consequently, increasing the LF/HF ratio, normalizing the frequency conditions in HRV.

***Discussion*:** In the frequency index, HF indicates the vagal activity, whereas LF indicates both systems with parasympathetic predominance. Before treatment, the dog had a low LF/HF ratio (0.46), indicating dysautonomia with parasympathetic stimulation. After therapy, the conditions of bradycardia and functional cardiac capacity were corrected, restoring ANS, due to the serum recovery of thyroid hormones. This study reported the cardiac and autonomic effects of primary hypothyroidism untreated and treated with levothyroxine on a dog, that had intense bradycardia and abnormal stimulation of the parasympathetic tone, associated with episodes of 1st-degree AVB, ventricular ectopias, and 2nd-degree SAB. After therapy with a minimum dose of levothyroxine, there was a decrease in parasympathetic activity and an increase in sympathetic stimulus, correcting cardiac changes, and restoring the balance of ANS. As it is a simple, non-invasive, and safe tool that helps the clinician to understand cardiac autonomic modulation, it is recommended to adopt the Holter monitoring exam in cases of hypothyroidism cases to assess sympathetic-vagal balance and check potential cardiac risks.

Keywords: hypothyroidism, Holter monitoring, dysautonomia, levothyroxine, autonomic nervous system, cardiac risk.

Descritores: hipotireoidismo, monitoramento Holter, disautonomia, levotiroxina, sistema nervoso autônomo, risco cardíaco.

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INTRODUCTION

Hypothyroidism is a dysfunction in the hypothalamic-pituitary-thyroid axis that decreases the production of the hormones thyroxine (T_4) and triiodothyronine (T_3) by thyroid glands [20], being corrected by levothyroxine therapy [10,19,20]. This disease can be congenital [19], although rare [20], or acquired, which most canine cases are classified as acquired primary, due to lymphocytic thyroiditis or idiopathic thyroid atrophy that decrease the production of thyroid hormones [6,20]. Moreover, a high prevalence of circulating autoantibodies against thyroid hormones was found in Dalmatians, considered the 7th most prevalent breed [8].

The clinical signs are related to the metabolic rate, like lethargy, weakness, weight gain, unwillingness to exercise, and cardiovascular, neuromuscular and gastrointestinal changes [20]. In the cardiac system, 10% of dogs present bradycardia and arrhythmia, with a high risk of developing dilated cardiomyopathy and atherosclerosis [3,13,20] due to influence of thyroid hormones in the synthesis of cardiac proteins and the expression of cardiomyocyte structures [3,4,9].

As the heart is under constant influence from the autonomic nervous system (ANS), its modulation can be assessed by heart rate variability (HRV) [14,16,17,22]. For this, the Holter exam for 24 h is the most complete method for assessing cardiac rhythm [15-17], being commonly used in hypothyroidism human [5,11,23,24], due to the risk of arrhythmias and dysautonomia. However, reports in dogs are scarce [6,13,15].

We aimed to report the cardiac and autonomic effects of primary hypothyroidism untreated and treated with levothyroxine in a Dalmatian dog through Holter monitoring.

CASE

A 7-year-old female Dalmatian dog, weighing 36 kg, was referred to a private veterinary clinic in Fortaleza, Ceará (Northeast Brazil) due to apathy, weight gain, poor hair quality, lethargy, lack of response to playing commands and facial expression described as sad a year ago (Figure 1A). On physical examination, skin lesions were observed in the hind limbs and the final region of the spine, extending to the tail, which was alopecic. The temperature was 38.2ºC, the mucous membranes were moist pink, and the capillary filling time was less than 2 s, considered normal. On auscultation, bradycardia with heart rate (HR) between 40 to 50 bpm, apparently regular, was noted, in addition to a 3/6 mitral murmur and 2/6 tricuspid murmur.

Considering the dermatological and cardiac findings, hypothyroidism was suspected, and blood was collected to measure thyroid hormones. An increase in thyroid-stimulating hormone (TSH) levels (0.65 ng/mL; reference value - RV: 0.04-0.4 ng/mL) and a decrease in free T_4 (0.11 ng/mL; RV: 0.6-2.0 ng/mL) and total T_4 (0.44 ng/mL; RV: 1.2-4.0 ng/mL) levels showed that the patient had primary hypothyroidism. Thus, hormonal supplementation with a minimum dose of levothyroxine (Puran T4®)[1] [0.913 mg, every 12 h] was started indefinitely, in which the dog showed the remission of the clinical signs and improved the quality of life in 5 months of treatment.

To assess the impact of untreated and treated hypothyroidism on ANS, an HRV analysis was performed by Holter monitoring [24]. This method is considered the most complete to assess cardiac rhythm and the presence of abnormal complexes, verifying the autonomic condition [14,16,17,22]. Therefore, two Holter monitoring exams were performed, being one before treatment and the other after five months of levothyroxine therapy.

For this, the heart rate was monitored for 24 h, using a portable three-channel digital device (Cardio flash plus®)[2] containing electrodes. After trichotomy and cleaning with 70º alcohol in the thoracic region, the electrodes were fixed to the surface of the skin with adhesive tape. The electrodes were positioned in the following precordial leads: location between 5th and 6th intercostal spaces on the right (negative electrode) and left (positive electrode) sides; at the junction between the upper and middle 3rd of the chest, forming the X--axis; in the manubrium region (negative electrode) and xiphoid cartilage region (positive electrode), forming the Y-axis; location between the spinous T7 process (negative electrode) and the opposite ventral aspect (positive electrode), forming the Z-axis. To cover and protect the electrodes, a bandage was applied to the dog's chest, as well as to the digital recording device[2]. The 24 h electrocardiographic tracings were processed using the Cardio Manager S540 software[2] and always reviewed by the same veterinarian.

The parameters analyzed were the HRV electrical disturbances in the frequency domain, specifying the low frequency (LF; 0.04 a 0.15 Hz), and the high

frequency (HF; 0.15 0.4 Hz) waves components, which reflect, respectively, the sympathetic and parasympathetic ANS. Then, the LF/HF ratio was performed from the electrocardiographic record in 24 h of examination at each time of evaluation.

The Holter performed before treatment lasted 23 h 59 m, and ranged from 35 to 218 bpm, with an average HR of 75 bpm. It was observed that HR<50 bpm occurred during 05 h 20 min 36 s, and that HR>160 bpm occurred during 00 h 06 min 56 s. Still, 320 events of pauses longer than 2.0 s were recorded, with the longest pause being 2.3 s long (Figure 1B). Atrioventricular conduction 1:1 showed a PR interval predominantly within the normal range, ranging between 120 and 130 ms, and interspersed with moments of 1st-degree atrioventricular blocks (AVB), with a PR interval ranging between 140 to 160 ms, and generally associated with HR below 85 bpm (Figure 1C). The QT intervals were within the normal range for the canine species, ranging between 230 and 250 ms. No ST--segment depression or elevation events were recorded. There were zero supraventricular ectopic events and 6 ventricular ectopic events, in which 6 were isolated ectopias, zero paired, and zero tachycardias.

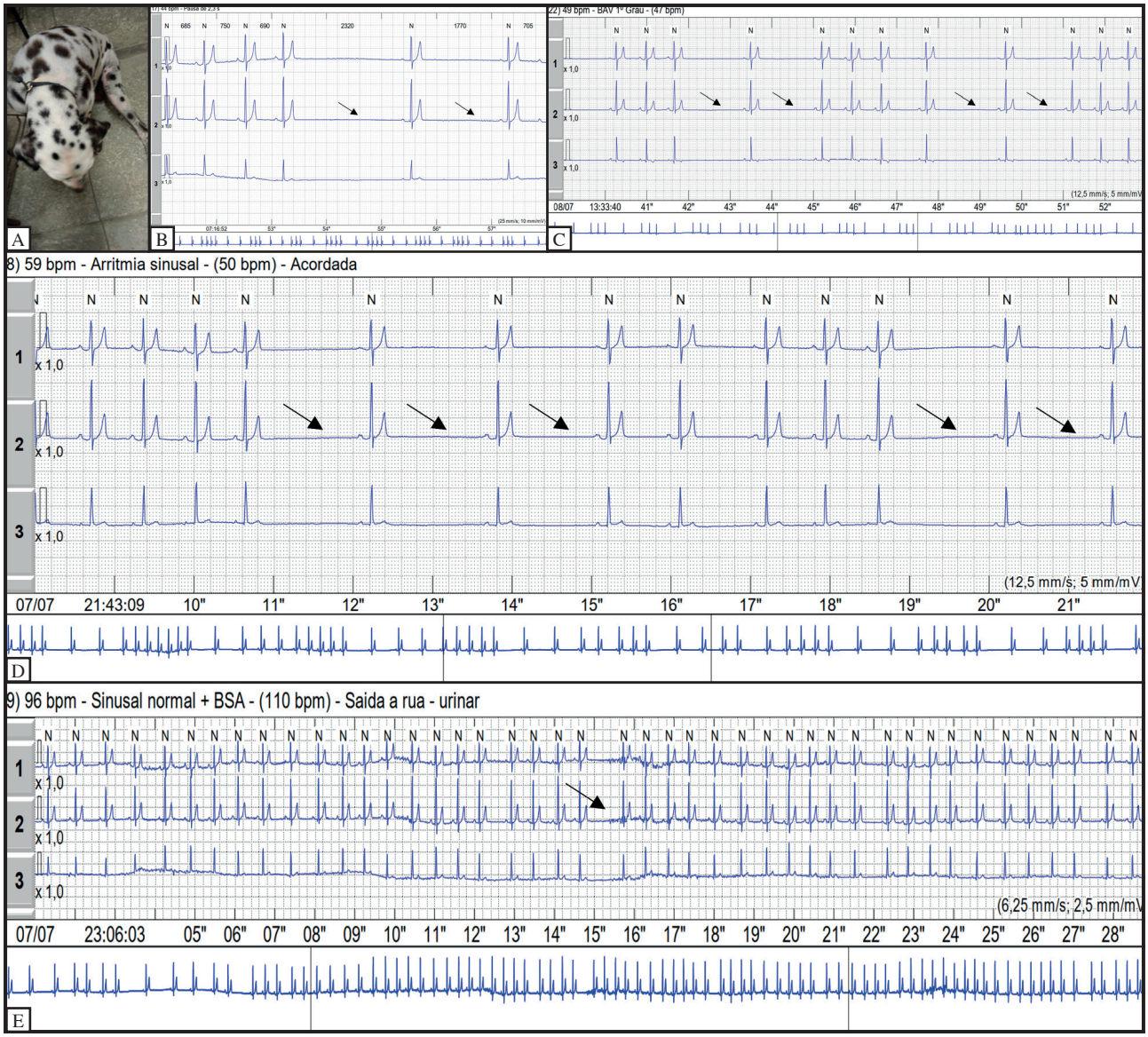

Figure 1. Primary hypothyroidism on a female Dalmatian dog with intense cardiovascular involvement, presenting fatigue after min in standing up (A) and alopecia in hind limbs. An electrocardiogram using the Holter method for 24 h before treatment revealed the following cardiac changes during the monitoring of beats per minutes (bpm; arrows): long pause of 2.3 s (B), presence of 1st-degree atrioventricular block (AVB) with heart rate (HR) below 85 bpm (C) and sinus arrhythmia (D). When going outside to practice urinating (E), the dog presented a sinoatrial block (SAB) between the normal sinus beats during HR of 96 bpm. These cardiac findings showed that the primary hypothyroidism significantly increased the parasympathetic tone, indicating that this endocrine disease altered the patient's autonomic nervous system.

In this way, it was concluded that the dog presented sinus arrhythmia (Figure 1D) associated with 2nd-degree sinoatrial block (SAB) (Figure 1E) and rare moments of sinus tachycardia. Premature multifocal ventricular extrasystoles, low incidence of ventricular electrical instability, and moderate to a high incidence of atrioventricular conduction disorders have also been identified. Additionally, ventricular repolarization was noted without the risk of myocardial hypoxia. Therefore, these findings showed that the parasympathetic tone of the ANS was significantly stimulated.

In turn, the Holter test performed after five months of levothyroxine therapy lasted 23 h 24 m, and ranged from 39 to >200 bpm, with an average HR of 89 bpm. It was observed that HR<50 bpm occurred during 02 h 06 min 13 s, and that HR>120 bpm occurred during 04 h 36 min 56 s. There were no significant pauses or blocks (Figure 2A), and the PR intervals were within normal limits, as were the QRS complexes and ventricular repolarization. The dog did not present supraventricular ectopia, and the presence of sinus arrhythmia (Figure 2B) was considered physiological. These findings showed that there was a

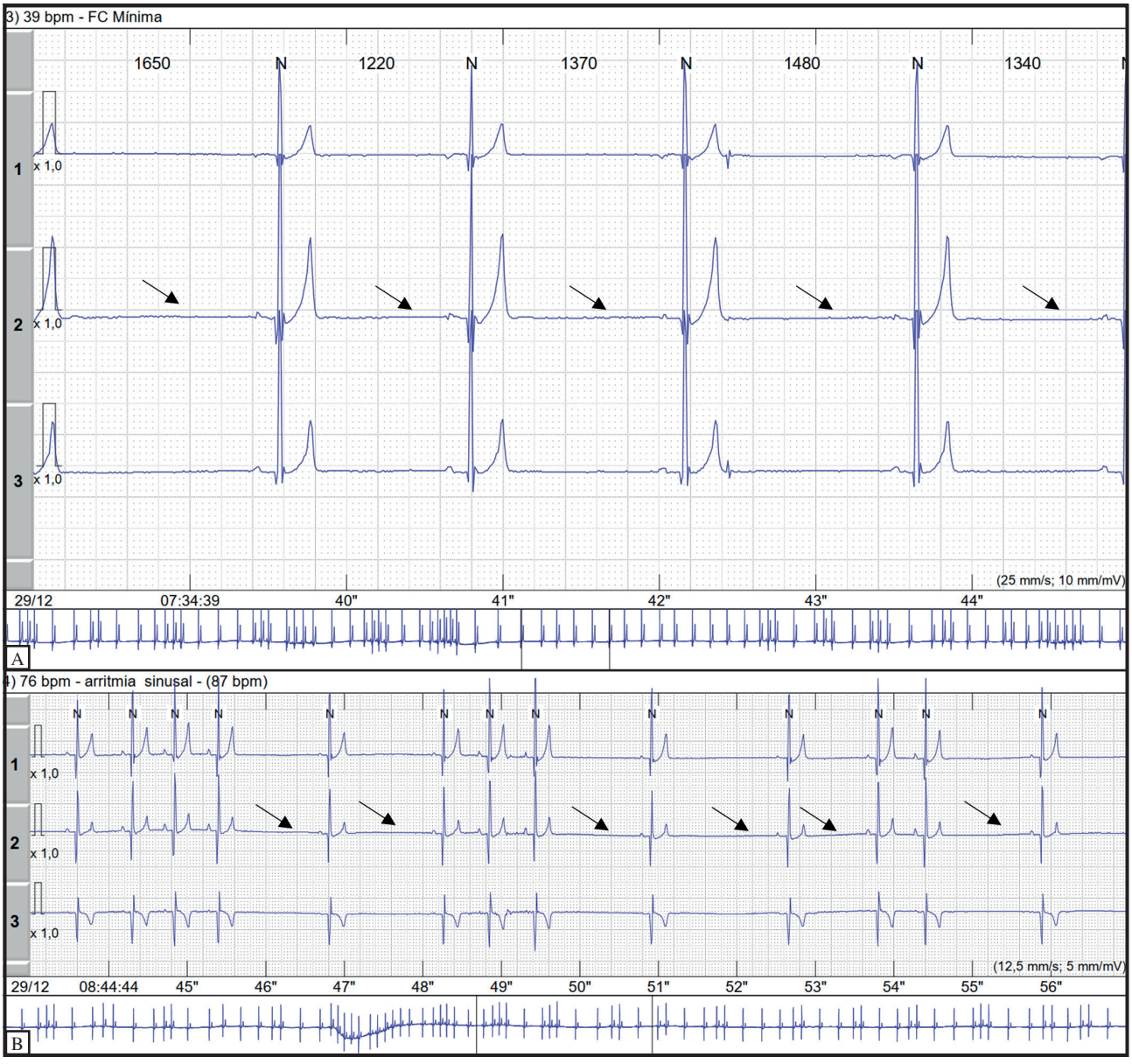

Figure 2. After 5 months of levothyroxine therapy, a new electrocardiogram by the Holter method for 24 h showed improvements in cardiac conditions. Minimum heart rate (HR) were observed with no ventricular ectopias or blocks (A), in addition to sinus arrhythmia during HR of 87 bpm (B), considered physiological. The absence of expressive stimulus of sympathetic or parasympathetic tones indicated that the hormonal therapy safely restored the balance of the autonomic nervous system.

Table 1. Heart rate variability (HRV) frequency-domain measures before and after five months of treatment with levothyroxine in a canine case of primary hypothyroidism.

Parameter (unit)	Values found in the canine patient		Reference values for canine species*
	Before treatment	After treatment	
LF power (ms^2)	974	1,202	1,182 - 1,565
HF power (ms^2)	1,887.5	510	432 - 751
LF/HF ratio (%)	0.46	2.36	2.21 - 2.74

LF: low frequency (0.04 - 0.15 Hz); HF: high frequency (0.15-0.4 Hz); *Values based in healthy dogs presenting body condition score number 5 [15] and in the calculation of the respective 95% confidence interval.

stimulus in the sympathetic tone, which restored HR and, therefore, the ANS balance.

In the comparative analysis of HRV in the frequency domain index (Table 1), it was observed that the hormone therapy with levothyroxine corrected cardiac changes by increasing the LF, decreasing the HF and, consequently, increasing the LF/HF ratio, normalizing the frequency conditions in the patient's HVR.

DISCUSSION

About 90% of the dogs with primary hypothyroidism present a decrease in total T_4 associated with an increase in 65-75% in TSH concentration, which is considered a marker for identifying this disease [18]. In the present report, the dog had high TSH and low levels of free T_4 and total T_4, characterizing primary hypothyroidism [18], which is one of the most common endocrine diseases in small animals [20].

It is known that the T_3 hormone plays a stimulating role in the synthesis of structural cardiac proteins, such as voltage-dependent potassium channels, β1-adrenergic receptors, sodium/potassium ATPase, among others [4], justifying the intense impact of untreated hypothyroidism on the cardiac system [3,24]. Thus, the cardiovascular system is strongly influenced by ANS [16], since, in an episode of an imbalance between sympathetic and parasympathetic ANS, that is dysautonomia [12], it would result in cardiac changes, such as arrhythmias, sinoatrial blocks [6], dilated cardiomyopathies [3] and even risk of tissue necrosis, due to abnormalities in the myocardial microarchitecture [13]. Signs of pause, arrhythmia, and blocks were observed on the dog's electrocardiography (Figure 1B-1E), representing cardiac risks and, therefore, requiring monitoring of the cardiac condition for detailed investigation [6].

In the HRV assessment, the cardiac indexes LF and HF in the frequency domain help the veterinarians to understand the sympathetic and parasympathetic components that regulate the heart. HF as an indicator of vagal activity and LF is an indicator of both autonomous systems with parasympathetic predominance [14,22]. In Holter monitoring before treatment (Table 1), the dog had reduced LF associated with high HF, which resulted in a low LF/HF ratio. Knowing that the LF/HF ratio represents the sympathetic-vagal balance [14], these findings showed dysautonomia with a predominance of parasympathetic tonus.

Thyroid hormones stimulate sympathetic activity, especially at the cardiac level [7], as they increase the response of catecholamines on the heart, due to the positive regulation of the sarcoplasmic reticulum Ca^{2+}-ATPase channels and β-adrenergic receptors [7]. Therefore, the dysautonomia caused by untreated hypothyroidism leads to an overlap of parasympathetic ANS in the cardiac system [3], due to the low serum concentration of T_3 and T_4 [6], as shown in the canine patient.

Of the cardiac autonomic dysfunctions reported in humans [5,23] and dogs [6] with hypothyroidism, the abnormal changes in HRV [6,11,23] were characterized by an increase in HF, indicating stimulating of vagal tone [23] and a decrease in LF, indicating stimulation of parasympathetic activity [14,22]. The decrease in the LF/HF ratio before the treatment of the dog indicated a low HRV, which may have occurred due to a significant reduction in baroreflex sensitivity [21], which end up impairing the control of heart rate and vascular sympathetic tone during untreated hypothyroidism [6]. In this way, hypothyroid patients have significantly higher cardiac risks [21], and the disease control through hormone therapy is essential to maintain the patient's health [6,10,23].

The treatment is based on hormonal supplementation with sodium levothyroxine, also known as "synthetic T_4" or "l-thyroxine" [5,20]. This hormone decreases TSH secretion in the hypothalamus-pituitary-thyroid axis [25] and, thus, restores the values of T_3 and T_4 to normal. Started treatment, it was noted improvements in the physical condition of the dog, that lost weight, weighing 10 kg after 5 months of therapy, and with the growth of shiny and less brittle hair in the alopecic areas.

At the cardiac level, the second Holter monitoring exam revealed improvements in heart rate. Considering that HR<50 bpm occurred during 05 h 20 min 36 s before treatment, it was observed that the time of occurrence of this parameter reduced to 02 h 06 min 13 s after 5 months of levothyroxine therapy, showing that the treatment corrected the bradycardia condition caused by hypothyroidism. Levothyroxine increases mean HR and P wave amplitude [10], correcting functional cardiac capacity and restoring ANS rebalancing, and the effects can already be seen in 3 months of therapy [23], due to the recovery of serum concentrations of T_3 and T_4 hormones.

This nervous restoration caused by levothyroxine therapy occurred due to the effect of thyroid hormones on cardiac function. It is known that the T_3 hormone binds to the numerous TRα and TRβ receptors present in cardiomyocytes, increasing the strength of systolic contraction [9]. Although the T_3 level was not measured in the dog, this hormone is mainly formed by the dissociation of T_4 in peripheral tissues, such as the liver and muscles, to supply energy to local cells [18].

Thus, a measurement of T_4 below the physiological level implies reduced levels of T_3, which explains the behavioral changes observed before treatment, such as apathy, fatigue, and low stimulus to play commands. Mental dullness and lethargy are 2 of the most frequently documented behavioral abnormalities in hypothyroid dogs, which typically resolve within a few weeks of thyroid hormone supplementation [20]. After 5 months of levothyroxine therapy, the patient showed a significant decrease in the signs of tiredness and lethargy and became active and alert. This improvement was the result of the restoration of thyroid hormone levels, since, when reduced, decrease low metabolic rate, causing lethargy, mental confusion, and inactivity [20]. In cases of untreated hypothyroidism, the decrease of energy to local cells [18] can lead to hypometabolism, which can worsen for myocardial necrosis in severe cases [13].

Thus, in a comparative analysis of Holter monitoring exams, it was observed significant changes in the patient's cardiac condition before and after treatment with levothyroxine. During untreated hypothyroidism, the dog showed intense abnormal stimulus of the parasympathetic tone, due to a change in sinus function, in which the frequency was reduced and arrhythmic (Figure 1D). The altered conduction of the sinoatrial node can be impaired or blocked by disease or increase in vagal activity [2], which corresponded to the high values in HF (Table 1). Thus, the intranodal and sinoatrial conductions become slow, leading to bradycardia [2,6], as observed before treatment because of the low values in LF.

The episodes of 1st-degree AVB (Figure 1C) and 2nd-degree SAB resulted from the increase in the refractory period caused by the inhibition of L-type voltage-dependent calcium channels [1,6], showing that the dog had altered atrioventricular conduction due to increased parasympathetic tone. Additionally, the 6 episodes of ventricular ectopias observed in the patient require constant cardiac monitoring, because, although rare in dogs [6], they can be predictors of death after exercise [1].

Once treatment with levothyroxine started, the dog showed a decrease in parasympathetic activity (HF) associated with an increase in the sympathetic tone stimulus, which allowed the restoration of HR without recurrence of episodes of 2nd-degree SAB and 1st-degree AVB. These findings demonstrated that the use of levothyroxine after 5 months of therapy in primary hypothyroidism corrected cardiac changes, restoring the ANS balance. There are other therapeutic options, such as the use of liothyronine sodium (synthetic triiodothyronine), which is indicated when levothyroxine therapy failed to obtain a therapeutic response [20]. However, there are no studies on the effects of the cardiovascular risks of this drug on canine hypothyroidism yet.

Considering that the Holter monitoring exam is a simple and non-invasive tool that helps the veterinarians to understand cardiac autonomic modulation [6,14,16,17], it is recommended to use this exam in the clinical routine in cases of hypothyroidism for monitoring the cardiac risk and the ANS imbalance. Additionally, studies with other drugs for the treatment of hypothyroidism, such as liothyronine sodium,

deserve to be investigated regarding the effects on the cardiac and autonomic systems, due to the lack of data.

This study reported the cardiac and autonomic effects of the untreated and treated primary hypothyroidism in a Dalmatian dog. During untreated hypothyroidism, the dog presented intense bradycardia and abnormal stimulation of the parasympathetic tone, associated with episodes of 2nd-degree SAB, 1st--degree AVB, and ventricular ectopias. After 5 months of a minimum dose of levothyroxine, this therapy decreased the parasympathetic activity and increased the stimulus of sympathetic tone, correcting cardiac changes, and restoring the ANS balance. Additionally, the cardiac evaluation by Holter monitoring is an auxiliary method recommended in the clinical routine for its simple and safe use during the assessment of sympathetic-vagal balance and checking of potential cardiac risks.

MANUFACTURERS

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