

## HEMODYNAMIC EFFECTS OF HYPOTHYROIDISM INDUCED BY ADMINISTRATION OF METHIMAZOLE TO EUTHYROID DOGS

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### Köpeklerle Methimazol Uygulanmasıyla Oluşan Hipotiroidizmin Hemodinamik Etkileri

**Özet:** Bu araştırma, methimazol'ün ötroid köpeklerin kardiyak fonksiyonlarının invaziv parametreleri üzerine olası etkilerinin saptanması amacıyla yapıldı. Çalışmada on adet ötroid köpek kullanıldı. Methimazol (30 mg/kg) uygulanmasından önce ve sekiz hafta sonra serum T<sub>4</sub>, T<sub>3</sub> ve TSH konsantrasyonları ve sol ventrikülün sistolik (LVSP) ve diyastolik basınçları (LVDP), kasılma (LVCT) ve gevşeme zamanı (LVRT) ölçüldü. Sekiz haftanın sonunda TSH konsantrasyonu önemli oranda artarken, serum T<sub>4</sub> ve T<sub>3</sub> konsantrasyonları, LVSP ve LVDP önemli bir şekilde azaldı. Bununla birlikte LVCT'deki artış önemli değildi. Kontrol ve hipotiroid köpeklerin LVRT arasında farklılık gözlenmedi. Elde edilen veriler, methimazol'ün köpeklerde serum tiroid hormon konsantrasyonlarının yanısıra sol ventrikül basınçlarında da önemli değişikliklere neden olduğunu gösterdi.

**Anahtar kelimeler:** Hemodinamik, Hipotiroidizm, Köpek, Methimazol.

**Summary:** This study was carried out in order to determine the possible effects of methimazole upon the invasive parameters of the cardiac functions of the dogs. Ten dogs were used in this study. In the beginning of the study and 8 weeks after orally administration of methimazole (30 mg/kg), serum T<sub>4</sub>, T<sub>3</sub> and TSH concentrations and contraction (LVCT) and relaxation times (LVRT), systolic (LVSP) and diastolic pressures (LVDP) of left ventricle were measured. After weeks, serum T<sub>4</sub>, T<sub>3</sub> concentrations, LVSP and LVDP were significantly decreased, while TSH concentrations were significantly increased. However, increasing in the LVCT was not important. No difference was observed between the LVRT of healthy and hypothyroid dogs. The results of the present study suggested that methimazole caused significant changes in serum thyroid hormone concentrations as well as the left ventricle pressures of dogs.

**Key words:** Hemodynamic, Hypothyroidism, Dog, Methimazole.

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### Introduction

Hypothyroidism is a common endocrine disorder in dogs caused by insufficient production and secretion of thyroid hormones as thyroxine "T<sub>4</sub>" and 3,5,3'-triiodothyronine "T<sub>3</sub>" (32). It is usually seen in female dogs between ages 2 and 6 years (17, 36, 38). The endocrine disorders occur in primary, secondary and tertiary types. Primary hypothyroidism is dysfunction of the thyroid gland, including lymphocytic thyroiditis, idiopathic follicular atrophy, thyroidectomy and other causes, and one of the most common endocrine diseases in dogs (9, 13, 45). Secondary hypothyroidism occurs when pituitary gland secretion of bioactive thyrotropin (TSH) is inadequate. Tertiary hypothyroidism arises from decreased hypothalamic thyrotropin-releasing hormone (TRH) (5, 31, 44).

In as much as thyroid hormone deficiency affects multiple metabolic processes of all body systems, clinical signs are variable and often non-specific (28). Due to the slow down in basal metabolism, clinical signs of the disease were seen. Hypothyroidism causes disorders in the skin, alimentary tract, muscles, nerves, urinary and reproductive systems (3, 38). However, heart diseases are one of the most common complications of hypothyroidism in dogs (12, 15, 19, 40). It is reported that hypothyroidism causes decreasing in heart contraction and diastolic functions, pericardial effusion and so heart insufficiency (2, 6, 14). Differences in electrocardiograph (ECG), echocardiography, cardiac enzymes and isoenzymes levels were reported in dogs induced experimentally hypothyroid (29, 35).

Myofibrillar swelling with loss of striation, interstitial fibrosis, mitochondrial disruption, lipid inclusion (35), and accumulation of mucopolysaccharide substances occurs on histo-pathological examination of the heart with hypothyroid (23).

Both invasive and non invasive cardiac changes have been observed in searches conducted on dogs with hypothyroid (9, 29, 39). The invasive cardiovascular differences could have been observed after administering sedatives. It is determined by also many studies that sedatives and anaesthetics causes cardiovascular changes in both healthy and unhealthy dogs (1, 34, 42). There are so many substances causing decrease in serum thyroid hormone concentrations and disturbing thyroxin synthesis (25). Methimazole which is one of these substances is suggested for the treatment of hyperthyroidism (27, 30).

It has been demonstrated that hypothyroidism induced by methimazole in portal hypertensive rats ameliorated the hyperdynamic circulation in a study (27). Another study described that rat left ventricular contractility was depressed by hypothyroidism (18). But the invasive cardiovascular effects of hypothyroidism induced by methimazole in euthyroid dogs have not been systematically investigated.

The purpose of this investigation was to test whether invasive parameters of cardiac function had changed in response to the administration of methimazole in euthyroid dogs.

## Material and Methods

### *Animals and experimental design*

Ten female (non-spayed) dogs of mixed breeds, with various body weights (18.3–24.8 kg) and ages (2 to 4 years old) were used in this study. These dogs were physically, haematologically, and biochemically healthy (i.e., normal routine haematological and biochemical parameters, including normal serum  $T_4$ ,  $T_3$  and TSH concentrations).

The dogs were kept in the individual boxes. Commercial dog food and water were supplied as ad libitum. All dogs were kept for 15 days under the same management conditions and antiparasitic drugs were administered against presumptive parasites.

After this stage, all dogs were given with 30 mg/kg body weight of methimazole, orally (Thyromazol, Abdi Ibrahim Ilac San. Tic. A.Ş., Istanbul, TR.) for 8 weeks in order to induce hypothyroidism. Before and 8 weeks after orally administration of methimazole, blood samples were obtained by jugular venipuncture and allowed to clot at 20°C. The serum was centrifugated in 2000 Xg for 5 minutes and stored at -20°C until  $T_3$ ,  $T_4$  and TSH analysis.

### *Measurements of serum $T_4$ , $T_3$ and TSH concentrations*

Serum  $T_4$ ,  $T_3$  and TSH concentrations were measured by commercially available kits for the determination of canine  $T_4$ ,  $T_3$  and TSH (Dignostic Products Corporation, Los Angeles, CA).  $T_4$  and  $T_3$  concentrations were evaluated in blood sera by solid-phase  $^{125}\text{I}$  radioimmunoassay. The sensibility of the commercial test kits were 0.25  $\mu\text{g/dL}$  ( $\mu\text{g/dL} \times 12.87 \rightarrow \text{nmol/L}$ ) and 7 ng/dL ( $\text{ng/dL} \times 0.01536 \rightarrow \text{nmol/L}$ ), respectively. Measurements were done by Gamma counter (Izocomp I, MGM. Inst., Hamden, USA) by reading single sample. Serum TSH concentrations were determined by using Monoclonal anti-TSH antibodies by Irma method. The sensibility of the commercial test kits were 0.03 ng/ml (13, 29, 32, 44).

### *Cardiac catheterization*

Cardiac catheterization was performed to all dogs before and 8 week after orally administration of methimazole. Dogs were fixed at lateral position and hair cut off from the medial face of right leg. This area was disinfected and anaesthetised locally by 3-5 ml lignocaine HCL 2% (Jetokain Lokal, Adeka Ilac San. LTD. STI. Samsun, TR). The skin was incised and *Art. femoralis* was carefully separated from surrounding tissues and a 5F pigtail catheter (Cordis Corporation, Miami, FL, USA.) was placed by punctuating. The catheter was send to the left ventricle via abdominal aorta. The outer edge of the catheter was connected to a polygraph (OSX-11, CGR, USA) by using connecting tubes. The place of the catheter was determined by observing the pressure slopes on the monitor. After being sure the catheter is in the left ventricle systolic and diastolic blood pressures were measured. Meantime ECG traces were observed on monitor. Pressure slopes and ECG traces were written on papers at a speed of 50 mm/sec. To avoid blood clotting in the catheter, physiologic saline solution with 10% heparin was used to wash the catheter. Pressure slopes written on paper were used to

calculate the contraction and relaxation times of left ventricle (22, 37).

### Statistical analysis

Data entry and analysis were performed using statistical Package for Social Science 6.0 for windows 95. Student's *T* test (two-tailed) of Graph PAD Instat were used for comparisons between the measurements obtained before and 8 week after orally administration of methimazole (10).

## Results

### Clinical findings

Dermatological defects (e.g., seborrhea, atopy, alopecia, scleroderma, opaque coloration of coat) were observed at the end of the 30<sup>th</sup> day of study. However, end of the study incoordination, anorexia, slimming temporary vomiting and diarrhea were observed on these dogs.

### Changes in blood serum

Serum  $T_4$ ,  $T_3$  and TSH concentrations of dogs before and 8 weeks after administration of methimazole were presented on Table 1. While serum  $T_4$  and  $T_3$  concentrations were initially  $3.77 \pm 0.89 \mu\text{g/dl}$  and  $67.0 \pm 10.43 \text{ ng/dL}$ , decreased significantly to  $1.53 \pm 0.32 \mu\text{g/dL}$  and  $34.5 \pm 3.87 \text{ ng/dL}$  after 8 weeks ( $p < 0.0001$ ), respectively. Serum TSH concentrations of euthyroid dogs was found to be significantly higher than the concentration of hypothyroid dogs ( $p < 0.001$ ).

**Table 1.** Serum  $T_4$ ,  $T_3$  and TSH concentrations of euthyroid dogs before and 8 weeks after administration of methimazole (mean  $\pm$  SD).

	$T_4$ ( $\mu\text{g/dL}$ )		$T_3$ (ng/dL)		TSH (ng/ml)	
	Weeks					
	0	8	0	8	0	8
Mean $\pm$ SD	3.77 $\pm$ 0.89	1.53 $\pm$ 0.32**	67.0 $\pm$ 10.43	34.5 $\pm$ 3.87**	0.17 $\pm$ 0.07	3.40 $\pm$ 1.12*
Min.	2.34	1.01	49.5	27.3	0.61	1.77
Max.	4.91	1.98	88.1	39.9	2.54	5.15

\*  $p < 0.001$  \*\* $p < 0.0001$

### Changes in cardiac functions

Diastolic and systolic blood pressure, contraction and relaxation times of the left ventricle of euthyroid dogs before and 8 weeks after administration of methimazole were presented on Table 2. At the beginning of the study, diastolic and systolic blood pressure of these dogs were  $124 \pm 6.4$  and  $88.4 \pm 5.8 \text{ mm/Hg}$ , respectively. In 8 weeks after methimazole treatment, these parameters decreased to  $72 \pm 5.8$  and  $52 \pm 7.6 \text{ mm/Hg}$ , respectively. Such decreases in the diastolic and systolic blood pressure of the left ventricle were important statistically ( $p < 0.001$ ). However, the increasing in the contracting periods of the left ventricle was no important. No difference was observed between the relaxation periods of the left ventricle of euthyroid and hypothyroid dogs.

**Table 2:** Diastolic and systolic blood pressure, contraction and relaxation times of the left ventricle of euthyroid dogs before and 8 weeks after administration of methimazole (mean  $\pm$  SD).

Parameters	Weeks	
	0	8
LVDP (mm/Hg)	124 $\pm$ 6.4	72 $\pm$ 5.8*
LVSP (mm/Hg)	88.4 $\pm$ 5.8	52 $\pm$ 7.6*
LVCT (mm/sec)	0.18 $\pm$ 0.04	0.20 $\pm$ 0.06
LVRT (mm/sec)	0.05 $\pm$ 0.006	0.06 $\pm$ 0.002

\* p &lt; 0.001

Left ventricle diastolic blood pressure (LVDP), left ventricle systolic blood pressure (LVSP), left ventricle contraction time (LVCT) and left ventricle relaxation time (LVRT).

### Discussion

Differences in serum thyroid concentration and invasive cardiac function in euthyroid dogs administered methimazole for 8 weeks were evaluated in this study. Diagnosis of hypothyroidism in dogs is made on the basis of clinical findings, results of routine laboratory and thyroid gland function tests, and response to thyroid hormone replacement (8). Determination of baseline serum concentrations of total thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) and provocative tests of thyroid secretory reverse (eg, TSH stimulation tests) have been the most common laboratory methods of assessing thyroid gland functions in dogs (8, 31). One of the studies have reported that measurement of serum free  $T_4$  and TSH concentrations was useful for diagnosis of hypothyroidism in dogs (32). In another study, it has been explained that hypothyroidism is generally assumed, if there are clinical symptoms with decreasing in serum free  $T_4$  and total  $T_4$  concentrations (17). In the present study, It was determined that serum total  $T_4$  concentrations were significantly decreased 8 week after orally administration of methimazole. Serum  $T_3$  concentration is frequently normal in hypothyroid dogs (41). However, Sendil and Mahzunlar (35) have emphasised that serum  $T_3$  concentrations significantly decreased in dogs with hypothyroidism experimentally induced. The same finding was present in this study.

Measurement of TSH concentration is a useful diagnostic test for evaluation of dogs suspected of having hypothyroidism (7). Assay of serum TSH is likely to prove helpful in the differential diagnosis of primary, secondary, and tertiary hypothyroidism in dogs (44). However, dogs with naturally developing hypothyroidism may be random fluctuation in TSH concentrations (4). In the last two decades, the diagnosis of primary hypothyroidism in dogs has been based on low plasma thyroxine concentration that is not responsive to thyrotropin (TSH) stimulation (4, 31, 44). Diagnosis of canine primary hypothyroidism is now often based upon the combination of a low thyroxine concentration and an elevated TSH concentration within a single plasma sample (16). We observed that cTSH concentrations significantly increased in dogs with hypothyroidism induced by methimazole .

Thyroid hormone has a significant effects on the heart (19, 23) and directly affects the heart and peripheral vascular system (11). An excessive deficiency of thyroid hormone can cause cardiovascular disease and aggravate many pre-existing condition (15). Gerritsen et al. (9) described that the frequency of primary hypothyroidism was higher in dogs with atrial fibrillation than in dogs without atrial fibrillation, and primary hypothyroidism could lead to additional cardiovascular changes. Changes in left ventricular function such as shortening fraction, velocity of circumferential fiber shortening, end systolic diameter and pre-ejection period in hypothyroid dogs have detected with non-invasive methods (29).

Hypothyroidism in rats induces a change from the V1 to the V3 isoenzyme, which contains less ATPase activity and thus is associated with decreased myocardial contractility (24). Lee et al. (18) described that the curvilinearity of the rat left ventricular end-diastolic pressure – volume relation was not determined by myosin isoenzyme per se, but by left ventricular contractility. The canine heart contains only the  $\beta$ -myosin (V3) isoenzyme (20). Serum T<sub>3</sub> decreases the heart transcription of the  $\beta$ -myosin heavy chain gene, leading to a decreasing in myosin V3 isoenzyme (23). The  $\beta$ -myosin heavy chain promoter activity is T<sub>3</sub> responsive in cultured myocytes and in vivo (26). Serum T<sub>3</sub> has a potential role for treatment of depressed myocardium in pigs (41). These factors may be more important in the pathogenesis of myocardial hypocontractility in hypothyroid dogs. Moreover, thyroid hormone has been used as an attractive therapy in humans with impaired hemodynamics and low serum T<sub>3</sub> concentrations (11).

Although a decrease in global systolic function at rest has been reported (6), in the other studies have no found diminished contractility in patient with hypothyroidism (2, 43). In spite of impaired hemodynamics including left ventricular diastolic and systolic blood pressure and low serum T<sub>3</sub> concentrations in our study, the contraction time of left ventricle was non-significantly detected an increase. We thought that the increase in contraction time of left ventricle could stem from myocardial hypocontraction or depression. An impairment in relaxation of left ventricle has been found in a study on a patient group with hypothyroidism (40). We have no found similar results. McMurphy et al. (21) reported that systolic arterial pressure measured by non-invasive methods, during 1.5 minimum alveolar concentration of isoflurane was significantly reduced. Similarly, in this study it was determined that diastolic and systolic blood pressure of left ventricle significantly decreased without performing general or inhalation anaesthesia in hypothyroid dogs. But many anaesthetic substances causes reduction of blood pressure (1, 34, 42). On the other hand, an increase in systolic blood pressure ( $p < 0.001$ ) without a significant change in diastolic blood pressure has been determined in a study on administration of L-Thyroxine for treatment of rats with hypothyroidism (33).

These findings suggest that serum thyroid hormone concentration, direct systolic and diastolic blood pressure of left ventricle occurred significant changes when Methimazole was given to dogs. In addition, left ventricular hypocontractility was determined in experimentally induced hypothyroid dogs, but changes in relaxation time did not happen.

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