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Original article

Cardiovascular problems in rabbits in reference to hypothyroidism – a four-year retrospective study

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Abstract

The effects of T4 are mainly manifested by positive ino- and chronotropism. The syndrome accompanying hypothyroidism in rabbits (impaired myocardial contractility and reduced ejection capacity) is caused by a deficiency of thyroid hormones - especially T4. The study group consisted of a total of 41 animals: 15 males and 26 females, ranging in age from 2 months to 8 years. with echocardiogram showing reduced fractional shortening (<30%), with normal results of heamatological and biochemical tests. Blood was collected in order to measure T4 level. Echocardiographic examinations were performed with two-dimensional (2D) imaging, M-mode measurements and the pulsed/colour-labelled Doppler technique. Statistical analysis was performed using Statistica 13.0. Correlations were determined: between serum thyroxine concentration and the value of the fraction of shortening in the groups: young animals (up to 5 years of age) and older animals, females and males, and sterilised and non-sterilised animals. Statistical analysis showed a positive correlation between T4 levels in the blood of the test animals and myocardial fractional shortening and heart rate and left-atrial to aortic ratio (LA/Ao) in the pre-treatment period. A positive correlation was also shown after dividing the patients into 2 groups based on their age (below 5 years vs. 5 years and over), sex (male and female rabbits) and fact of sterilization (yes/no). Our study unequivocally confirmed a positive correlation between the decreased serum T4 concentration and reduced fractional shortening, indicating decreased cardiac systolic function in hypothyroid rabbits.

Keywords: rabbit, hypothyroidism, echocardiographic examination, levothyroxine

Introduction

The thyroid is an endocrine gland directly adjacent to the trachea, located at the front of the neck just below the larynx (Kahaly et al. 2005, Asvold et al. 2007). In mammals, this paired gland consists of two connected lobes, the right and the left, made up of follicular epithelial cells (thyrocytes) and C cells. The secretion of thyroid hormones is regulated by the hypothalamus and pituitary gland. The hypothalamus produces thyroliberin (TRH – thyrotropin-releasing hormone), which stimulates thyroid cells of the pituitary gland to produce thyrotropic hormone (TSH – thyroid-stimulating hormone), which in turn stimulates the thyroid to produce and release thyroxine T4 and triiodothyronine (T3) into the bloodstream (Kahaly et al. 2005, Biondi and Cooper 2008, Gerdes and Iervasi 2010). These hormones are then bound in significant amounts by carrier proteins and transported in this form. Free thyroxine (fT4) accounts for 0.05% of total plasma T4, while free triiodothyronine (fT3) for 0.5% of total T3 (Asvold et al. 2007, Biondi and Cooper 2008, Gołyński 2012). Thyroid hormones are essential for the normal body functioning. Thyroxine plays a vital role, i.a., in heart function – it regulates the transcription of genes responsible for coding important structural and regulatory proteins associated with myocardial contractile function. Thyroid hormones and B-adrenergic receptor agonists affect the heart in a similar way. The effects of T4 are mainly manifested by positive ino- and chronotropism, while its deficiency leads to impaired myocardial contractility and reduced ejection capacity (Klein and Danzi 2007). Moreover, these hormones affect the cardiovascular system by influencing cardiac contractile protein synthesis, calcium pump, sodium-potassium pump and phospholamban, and have non-genomic effects by regulating the activity of ion channels in cardiomyocytes (Stephan et al. 2003, Rodondi et al. 2005, Asvold et al. 2007). Thyroid hormone receptors are located in all cells of the animal's body and therefore have a significant impact on the functions of the whole system (Asvold et al. 2007, Biondi and Cooper 2008). Hypothyroidism can be divided into primary and secondary types. Primary hypothyroidism is caused by chronic autoimmune thyroiditis, significant environmental iodine deficiency, irradiation of the neck area or excessive amiodarone administration, among others. Secondary hypothyroidism is an extremely rare component of hypopituitarism (Gerdes and Iervasi 2010). Hypopituitarism presents with a variety of symptoms with a predomination of dermatological disorders, such as dorsal alopecia. Other symptoms may include aggression, exercise intolerance, reduced cold tolerance or bradycardia (Stephan et al. 2003). The syndrome accompanying hypothyroidism is caused by a deficiency of hormones of this organ – in rabbits especially T4 (Kopański 1984, Gołyński 2012, DiGeronimo and Brandao 2020). The cardiovascular disorder characteristic of hypothyroidism is a reduced positive inotropic effect (Rodondi et al. 2005, Asvold et al. 2007, Pingitore et al. 2008). Affected animals present such symptoms as reduced physical activity, pale mucous membranes, low weight gain and dermatological problems (DiGeronimo and Brandao 2020). Over the past years, there have been more and more cases of hypothyroidism in rabbits (DiGeronimo and Brandao 2020, Ziętek et al. 2021); therefore, this study aims to determine the frequency of reduced fractional shortening in rabbits with hypothyroidism.

Materials and Methods

Animals

The study was conducted in the years 2019–2022. It included 177 rabbits with various cardiac disorders:

- dilated cardiomyopathy (DCM) – 42 individuals,
- mitral valve degenerative disease (MMVD) – 22,
- ventricular septal defect – 9,
- pulmonary stenosis (PS) – 11,
- aortic stenosis (AS) – 5,
- patent ductus arteriosus (PDA) – 8,
- neoplastic lesions – 16,
- cardiac tamponade – 18 animals.

The further studies included only the animals with echocardiogram showing reduced fractional shortening FS (<30%) calculated using M-mode, with normal results of basic biochemical tests (i.e. aspartate transaminase AST, alanine transaminase ALT, alkaline phosphatase AP, UREA, creatinine CREA, total bilirubin BIL T) and haematological tests. The group consisted of a total of 41 animals: 15 males and 26 females, ranging in age from 2 months to 8 years (the average age was 26 months in males and 24 months in females). In the group of 41 animals qualified for the study, two females and two males were older than 5 years, the other rabbits were younger. 15 females were sterilised (36.5% of the total study group), 11 were not sterilised (26.8%), eight males were sterilised (19.5%) and seven were not sterilised (17%). A summary of the animals is presented in Table 1.

The animals included in the study were pets receiving regular preventive care against ecto- and endoparasites. All rabbits were fed commercial foods, dried herbs, fresh vegetables and hay, and were provided with constant access to water. All animals were subjected to a routine clinical examination. All of them presented weakened heart tones on auscultation and decreased physical activity.

Table 1. The rabbits used in the study (FS: fractional shortening; LA/Ao: left atrial to aortic ratio; HR: Heart rate).

RABBIT No	SEX	AGE (months)	STERILIZATION	FS (%) before treatment	T4 (mg/dl) before treatment	LA/Ao before treatment	HR (bpm) before treatment	FS (%) after treatment	T4 (mg/dl) after treatment	LA/Ao after treatment	HR (bpm) after treatment
1	♀	12	no	28	6	1.44	211	34	6.8	1.37	221
2	♀	10	yes	26	6.9	1.42	189				
3	♂	36	no	29	5.8	1.52	202	35	7.6	1.41	209
4	♀	11	yes	24	5.5	1.46	184	34	6.5	1.39	204
5	♀	24	no	29	3.6	1.36	233	28	6.9	1.37	235
6	♀	5	no	28	5.6	1.45	187	37	7.2	1.38	199
7	♀	36	yes	22	5	1.49	202	35	7.8	1.41	209
8	♂	36	no	19	3.4	1.44	231	27	6.3	1.43	235
9	♀	11	yes	25	5.1	1.41	209	34	6.8	1.4	211
10	♂	60	yes	19	4.7	1.43	211	35	6.9	1.41	213
11	♀	48	yes	22	4.4	1.36	176	36	7.8	1.35	201
12	♂	12	yes	26	4.8	1.43	199	33	6.9	1.41	205
13	♂	36	no	29	5	1.43	203	36	7	1.38	212
14	♀	12	yes	27	5.4	1.41	199	36	7.1	1.38	217
15	♀	96	no	25	4.2	1.44	207	33	6.5	1.43	207
16	♀	24	yes	29	6.1	1.4	214	29	6.7	1.41	217
17	♂	8	yes	24	6	1.34	198	34	6.8	1.33	205
18	♀	4	yes	28	6.6	1.37	200				
19	♂	24	yes	25	5.5	1.45	203	33	7.5	1.43	205
20	♂	36	no	28	8	1.34	207				
21	♂	12	yes	27	6.1	1.43	204	38	7.8	1.38	209
22	♀	12	yes	25	5.9	1.46	221	31	6.7	1.44	223
23	♀	9	no	24	4.5	1.47	192	35	7	1.42	200
24	♀	24	yes	29	4.8	1.53	188	35	6.4	1.47	197
25	♂	7	no	28	5.5	1.49	178	36	6.7	1.42	189
26	♀	36	no	23	3.9	1.6	181	28	5.8	1.51	194
27	♀	12	yes	29	6.2	1.49	199	35	7.5	1.43	208
28	♂	12	no	19	3.5	1.51	179	26	6	1.48	188
29	♂	18	yes	29	6.2	1.44	201	31	6.5	1.44	214
30	♀	11	no	28	6.5	1.39	231				
31	♀	8	no	25	6.1	1.48	203	31	6.6	1.47	214
32	♀	36	yes	28	6.3	1.39	197	35	6.9	1.38	202
33	♀	24	no	27	5.5	1.41	234	31	6.7	1.41	237
34	♀	84	yes	24	5.3	1.52	194	32	6.4	1.48	200
35	♀	24	no	22	3.7	1.56	180	28	4.5	1.54	193
36	♀	11	yes	25	4	1.43	195	33	6.7	1.43	201
37	♂	3	no	18	3.8	1.53	179	27	4.8	1.49	180
38	♂	7	yes	22	3.9	1.48	177	30	6.4	1.46	185
39	♀	18	no	28	5.7	1.43	188	36	6.8	1.43	197
40	♀	24	yes	28	5.2	1.4	203	33	6.7	1.39	207
41	♂	84	yes	29	7.9	1.42	211				

Blood examination

Blood was collected from all rabbits in order to measure T4 thyroxine level using a VCheck V200 analyser. The physiological T4 concentration was established as the range of 6.4 to 8.3 mg/dl.

Cardiological examination

Echocardiographic examinations were performed on the animals in the supine position using an Esaote Mylab Class C ultrasound machine with a PA023 4-12 MHz phased-array multifrequency cardiac transducer. Each time, the myocardial structure and function were assessed. The examinations were performed with two-dimensional 113 (2D) imaging, M-mode measurements and the pulsed/colour-labelled Doppler technique. Two-dimensional imaging included long-axis and short-axis imaging planes from the right and left parasternal acoustic windows. Pulmonary artery and aorta flow measurements were taken. Left atrial and aortic diameters were measured to determine the ratio of the aorta to the left atrium. Additionally, HR was assessed in the ECG examination. The following measurements were taken in M-mode examination of the left ventricle:

- left ventricular lumen in diastole (LVDd),
- left ventricular lumen in systole (LVDs),
- interventricular septal thickness in diastole (IVSd),
- interventricular septal thickness in systole (IVSs),
- left ventricular posterior wall thickness in diastole (PWd),
- left ventricular posterior wall thickness in systole (PWs),
- fractional shortening (FS).

A range of 30.0% to 42.9% was considered normal values for fractional shortening (FS).

Statistical analysis

Statistical analysis was performed using Statistica 13.0. Correlation were determined: between serum thyroxine concentration and the value of the fraction of shortening, ratio of the aorta to the left atrium (LA/Ao), Heart Rate (bpm) in the groups:

- young animals (up to 5 years of age) and older animals (over 5 years of age),
- females and males,
- sterilised and non-sterilised animals.

Values of analysed parameters: FS (%) and T4 (mg/dl), ratio of the aorta to the left atrium (LA/Ao) and Heart Rate (bpm) were put in MS Excel. Within groups, Pearson correlation values (r) for the FS, T4, LA/Ao and HR parameters were calculated separately for values obtained before and after treatment with levothyroxine. The effects of therapy, expressed as the difference between the post- and pre-treatment values, were also checked. Results were considered statistically significant when the p-value $p<0.05$.

The study was conducted in accordance with the Directive of the European Parliament on the protection of animals used for scientific purposes (Directive 2010/63/EU). All owners of the rabbits agreed to include them in the study. Blood sampling was a part of the clinical procedure – no Ethic Commission Agreement was required.

Results

In the biochemical examination, a decrease in thyroid hormone levels below normal (6.4 mg/dl) was found in 36 of the 41 rabbits studied, representing 87.8% of the animals included in the study (Table 1). These included 10 unsterilised females (T4 blood concentration range was 3.6-6.1 mg/dl), 13 sterilised females (4.0-6.3 mg/dl), and six unsterilised males (3.4-5.8 mg/dl) and seven sterilised males (3.9-6.2 mg/dl). In all these individuals, echocardiography revealed a decrease in fractional shortening (<30%). Treatment with levothyroxine was implemented at a dose of 1.5 µg/kg q 12 h PO. After one month of treatment, the animals were subjected to a follow-up echocardiogram and their serum T4 levels were determined again. Introduction of the treatment resulted in an improvement in left ventricular systolic function and an increase in the T4 concentration in 29 rabbits, representing 70.73% of the animals included in the study. In one animal (rabbit no. 5), the reduced fractional shortening persisted, while the T4 concentration was within the physiological norm. In another animal (rabbit no. 16), the values of both examined parameters were still below physiological norms despite the undertaken treatment. On follow-up echocardiography, the remaining M-mode values did not change significantly, suggesting no change in left ventricular myocardial thickness with increased myocardial contractile force. Statistical analysis showed a positive correlation ($r=0.630$) between T4 levels in the blood of the test animals and myocardial fractional shortening in the pre-treatment period. The calculated values were statistically significant ($p = 0.000$) (Fig. 1).

After introduction of the treatment, results were similars ($r=0.711$, $p=0.000$) (Fig. 2). After dividing the patients into 2 groups based on their age (below 5 years vs. 5 years and over), a similar result was obtained for 37 younger animals ($r=0.634$, statistically significant $p=0.000$). There were only 4 individuals in the group of older animals, and the number of animals was insuf-

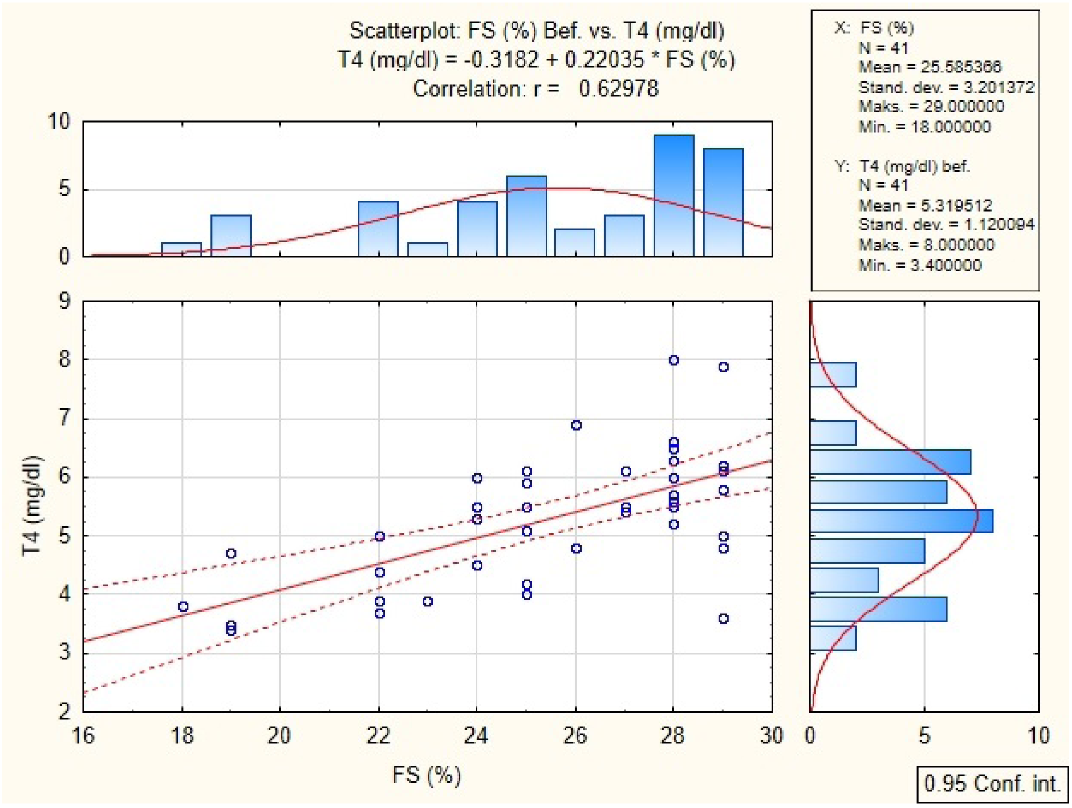

Fig. 1. A positive correlation between T4 levels in the blood of the test rabbits and myocardial fractional shortening in the pre-treatment period.

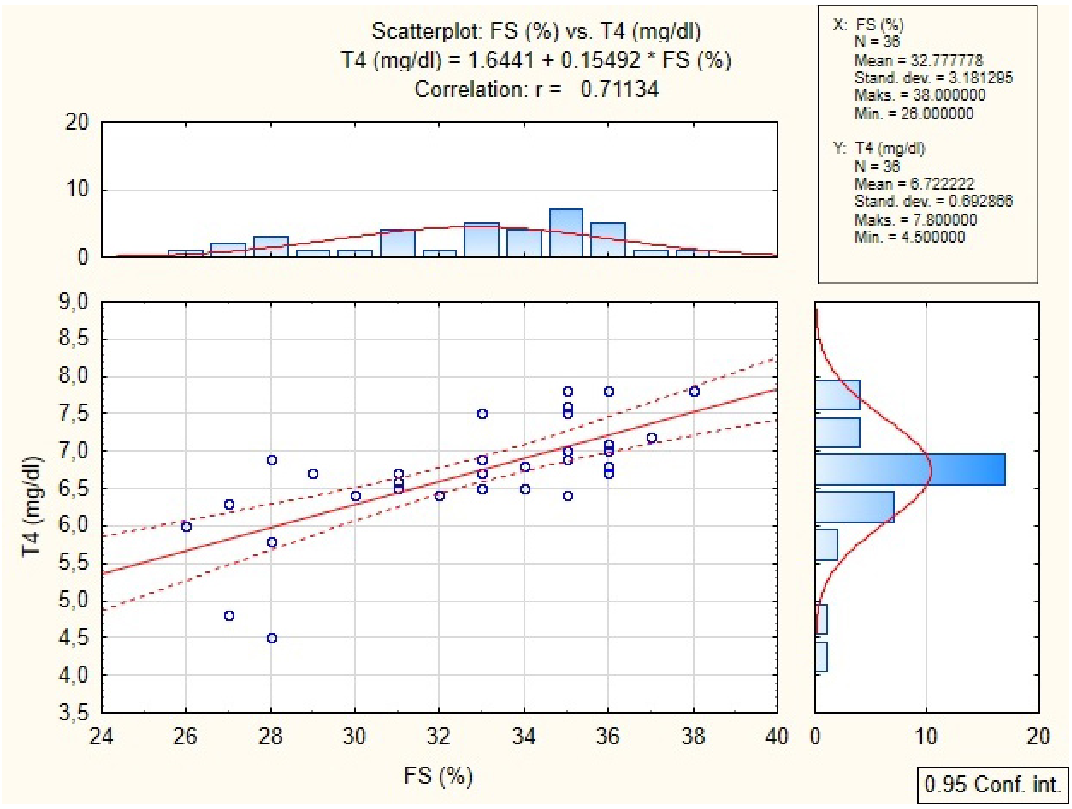

Fig. 2. A positive correlation between T4 levels in the blood of the test rabbits and myocardial fractional shortening in the post-treatment period.

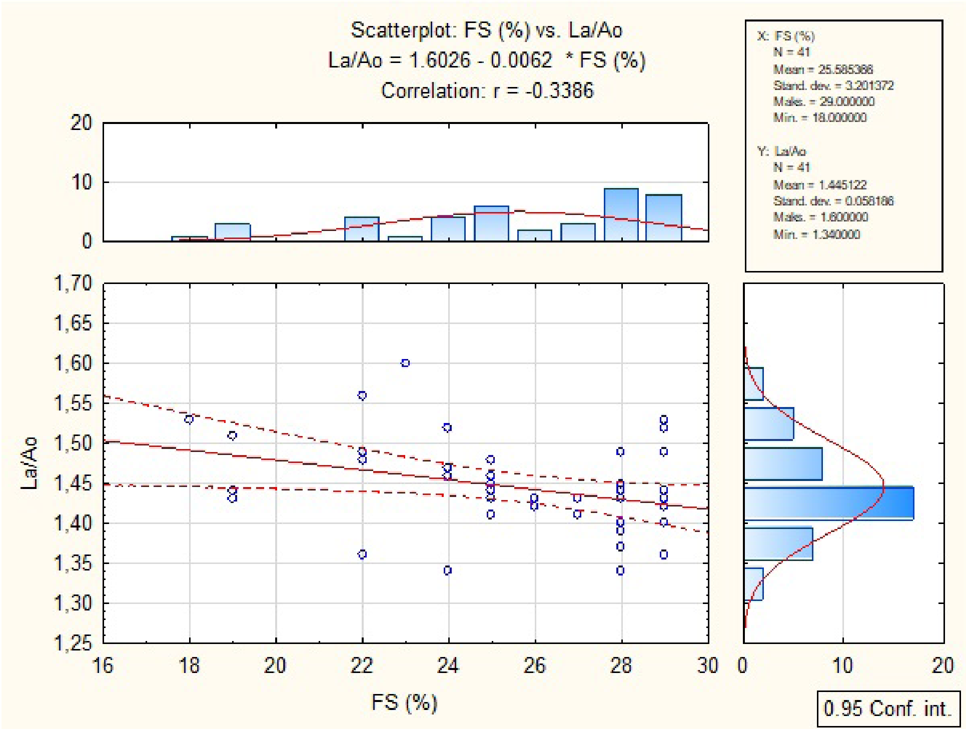

Fig. 3. A negative correlation between LA/Ao of the test rabbits and myocardial fractional shortening in the pre-treatment period.

ficient. A positive correlation was also shown after introduction of the treatment between the increase in the T4 concentration and the increase in the shortening fraction values in both age groups (r=0.714 and p=0.000 in the younger group). Considering the sex of the animals, the correlation between the decrease in the T4 concentration and the decrease in the shortening values in the pre-treatment period was lower in the females (26 animals; r=0.471) than in the males (15 animals; r=0.766). Nevertheless, it was statistically significant in both groups (p=0.015 in females and p=0.001 in males). After introduction of the treatment, a positive correlation was shown between the increase in the T4 concentration and the increase in the fractional shortening values in in females (r=0.645) and males (r=0.795). It was statistically significant in both groups (p=0.001). Determining the correlation between the decrease in the T4 concentration and the decrease in the shortening values in the groups of sterilised and unsterilised rabbits at the time of diagnosis revealed statistical significance in males, both castrated (r=0.745, p=0.034) and uncastrated (r=0.783, p=0.037). After introduction of the treatment, a positive correlation between the increase in the T4 concentration and the increase in the fractional shortening values was shown in the group of sterilised females (r=0.648, p=0.043) and sterilised males (r=0.806, p=0.029).

The group of animals with analysed parameters: ratio of the aorta to the left atrium (LA/Ao) and Heart Rate (bpm) after treatment was smaller and consisted a total of 36 animals (Table 1). Statistical analysis showed a negative correlation (r=-0.3386) between LA/Ao of the test animals and myocardial fractional shortening in the pre-treatment period. The calculated values were statistically significant (p = 0.030) (Fig. 3). After introduction of treatment, results were similars (r=-0.5930, p=0.000) (Fig. 4).

Statistical analysis of the Heart Rate of the test animals and myocardial fractional shortening in the pre-treatment period showed a positive correlation (r=0.28107) in the pre-treatment period (Fig. 5) and a negative correlation after treatment (r=-0.0376) (Fig. 6).

Correlations between T4 levels in the blood of the test animals and ratio of the aorta to the left atrium (LA/Ao) and T4 levels in the blood of the test animals and their Heart Rate, in both periods (pre- and post-treatment) are shown in Fig. 7-10.

All correlations obtained through statistical analysis of data in our research are collected in Fig. 11.

Discussion

Hypothyroidism is a syndrome of symptoms caused by T3 and T4 deficiency (Biondi and Cooper 2008). This disorder cannot be cured, but measures can be taken to minimise the symptoms and significantly improve the patient's quality of life. According to Tilley et al. (2010) and Pasławska et al. (2020), hypothyroidism in dogs very often results in a reduction of the

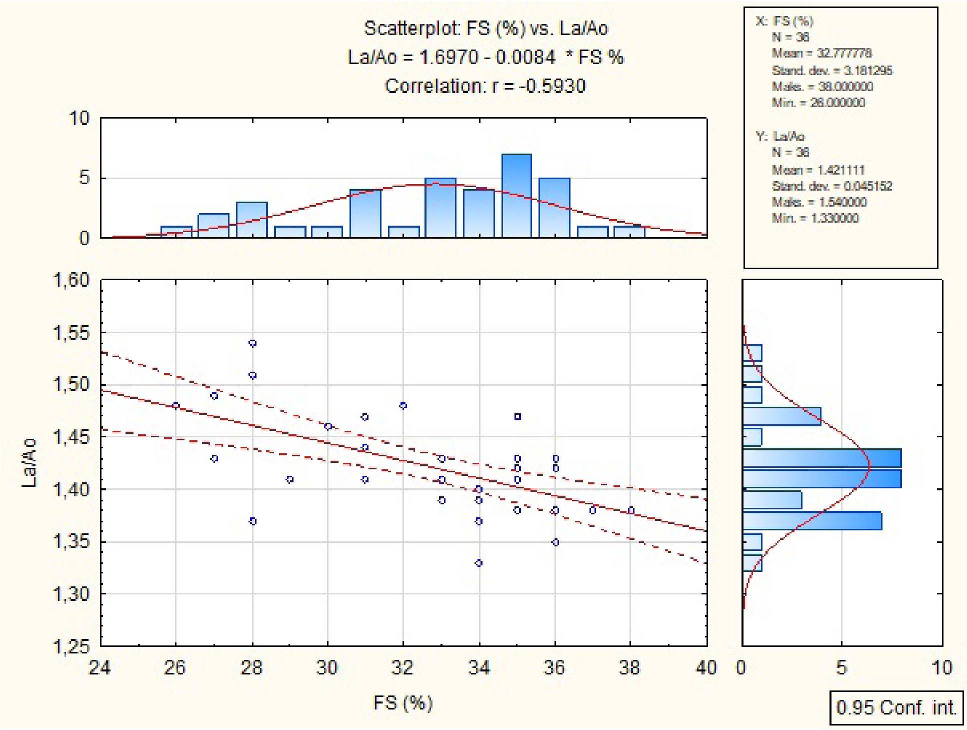

Fig. 4. A negative correlation between LA/Ao of the test rabbits and myocardial fractional shortening in the post-treatment period.

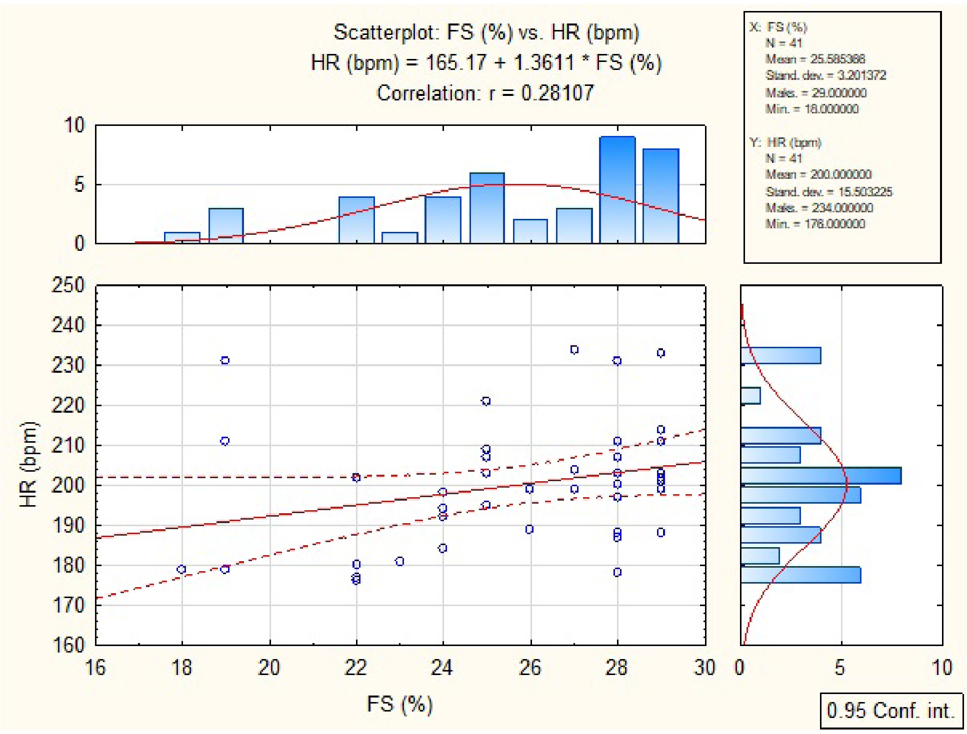

Fig. 5. A positive correlation between Heart Rate of the test rabbits and myocardial fractional shortening in the pre-treatment period.

fractional shortening and ejection fraction – similar to that seen in rabbits in our study. It should be emphasised that none of the patients included in the study showed any abnormalities of the shell or nervous system, apart from the cardiovascular symptoms. There are no data in the available literature on the influence of hypothyroidism on cardiac systolic function in lagomorphs, which was the reason behind this study. In available literature there is no reference ranges of diastolic function of the heart of rabbits, so it was not possible to measure, and correctly interpreted of this parameter. Kahaly and Dillmann (2005) showed that

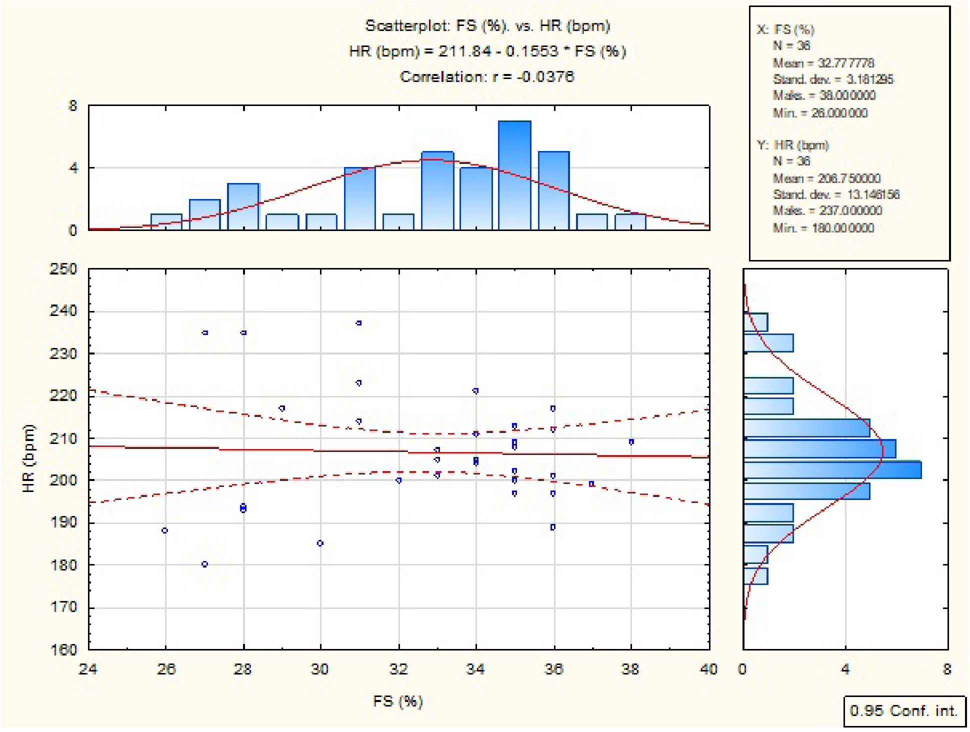

Fig. 6. A negative correlation between Heart Rate of the test rabbits and myocardial fractional shortening in the post-treatment period.

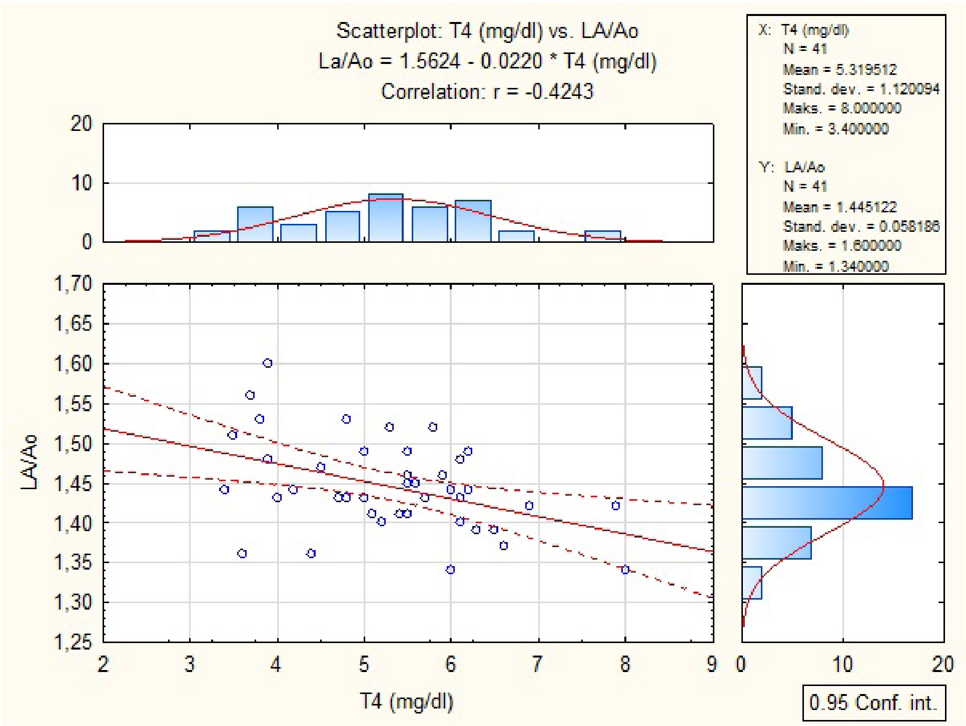

Fig. 7. A negative correlation between T4 levels in the blood of the test rabbits and ratio of the aorta to the left atrium (LA/Ao), in the pre-treatment period.

a typical example of the effect of T4 on the contractility of rabbit myocardial cells is the induction of changes in the quantitative distribution of myosin heavy chain isoforms. It was also found that thyroid hormones affect the expression of the gene encoding the a-MHC isoform and contribute to increased production of myosin, a protein that is part of contractile thick fibres. Statistical analysis of the results of our study did not show that sex, age or a history of sterilisation had any effect on the development of hypothyroidism or reduced fractional shortening. On the other hand, a positive correlation between the decreased serum T4 concentration and

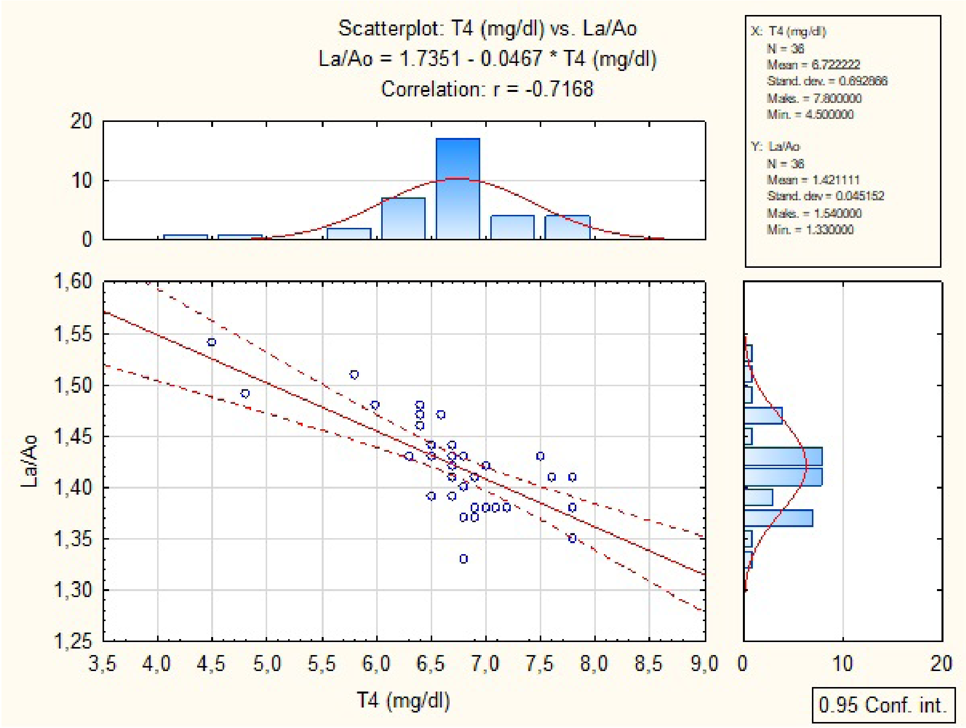

Fig. 8. A negative correlation between T4 levels in the blood of the test rabbits and ratio of the aorta to the left atrium (LA/Ao), in the post-treatment period.

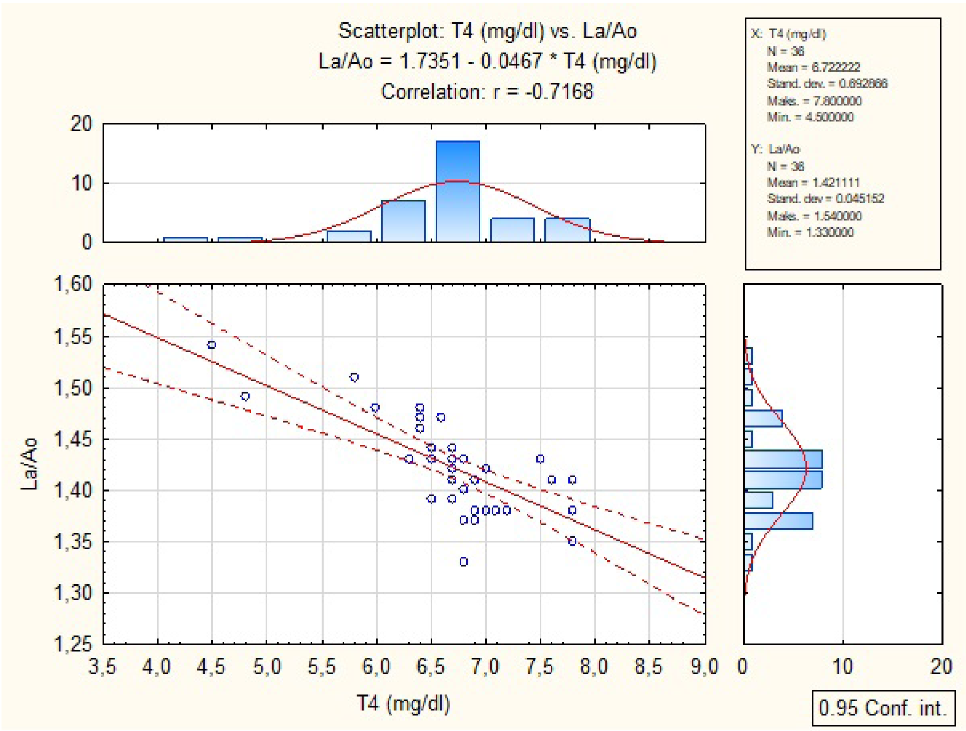

Fig. 9. A positive correlation between T4 levels in the blood of the test rabbits and Heart Rate in the pre-treatment period.

reduced fractional shortening 211 was unequivocally confirmed, indicating decreased cardiac systolic function in hypothyroid rabbits. Hypothyroidism treatment includes administration of levothyroxine at a dose of 1.5 µg/kg q 12 h PO. If cardiovascular disorders develop, oxygen therapy is also required in extreme cases, as well as the introduction of pimobendan at a dose of 0.25 mg/kg bw q 8 h PO to improve systolic function. Some cases of this disorder may be recurrent, so periodic cardiovascular follow-ups and routine blood tests must be performed (Ziętek et al. 2021). In our study, treatment with levothyroxine alone

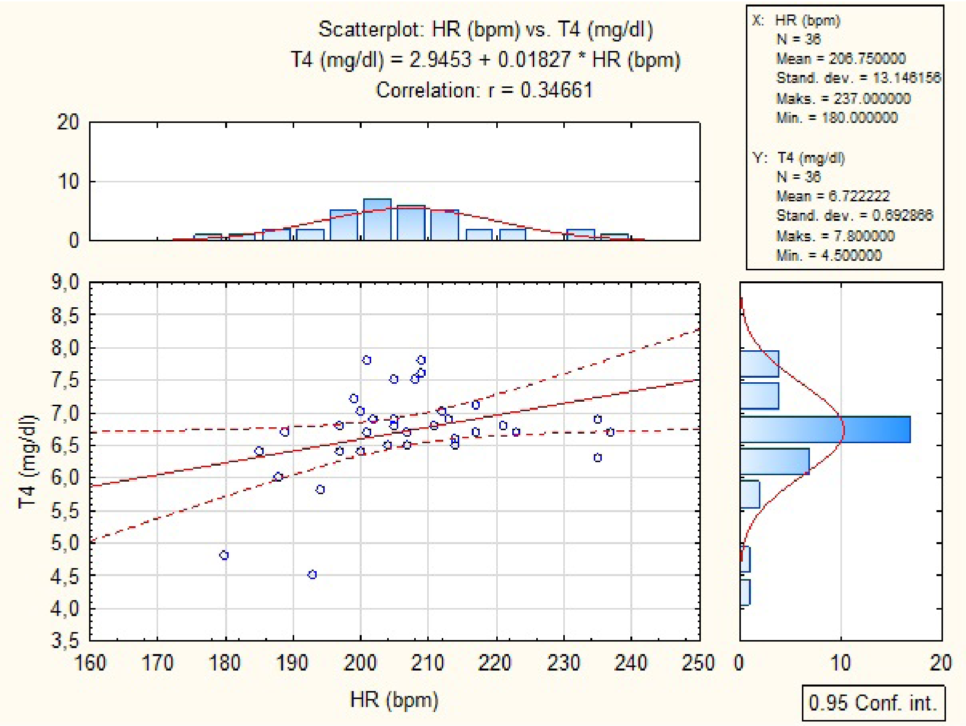

Fig. 10. A positive correlation between T4 levels in the blood of the test rabbits and Heart Rate in the post-treatment period.

		PRE-TREATMENT PERIOD		
	FS (%)	T4 (mg/dl)	LA/Ao	HR (bpm)
FS (%)		0,630	-0,339	0,281
T4 (mg/dl)	0,630		-0,424	0,230
LA/Ao	-0,339	-0,424		-0,467
HR (bpm)	0,281	0,230	-0,467	
		POST-TREATMENT PERIOD		
	FS (%)	T4 (mg/dl)	LA/Ao	HR (bpm)
FS (%)		0,711	-0,593	-0,038
T4 (mg/dl)	0,711		-0,717	0,347
LA/Ao	-0,593	-0,717		-0,427
HR (bpm)	-0,038	0,347	-0,427	

Fig. 11. Correlations between variables in pre- and post-treatment period.

improved myocardial contractility in 70.73% of patients, indicating the efficacy of such management.

This paper aimed at presenting the effects of hypothyroidism on myocardial function in rabbits, which suffered from myocardial contractility in the course of the disorder, as revealed on echocardiography. Levothyroxine treatment can result in stabilisation of the patients suffering from that disorder. Decreased fractional shortening is an increasingly frequently diagnosed – albeit undescribed in the literature – complication of hypothyroidism, and its development makes the diagnostic process and treatment much more difficult. Knowing that such a disorder may appear in rabbits, a veterinarian can implement appropriate management early, often saving the patient's life.

References

Asvold BO, Bjoro T, Nilsen TI, Vatten LJ **(2007)** Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. J Clin Endocrinol Metab 92: 841-845.

Biondi B, Cooper DS **(2008)** The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 29: 76-131.

DiGeronimo PM, Brandão J **(2020)** Updates on thyroid disease in rabbits and guinea pigs. Vet Clin North Am Exot Anim Pract 23: 373-381.

Gerdes AM, Iervasi G **(2010)** Thyroid replacement therapy and heart failure. Circulation 122: 385-393.

Gołyński M **(2012)** Structure and functions of the thyroid gland – details important for a practicing physician. In: Gołyński M (ed) Thyroid diseases in dogs. Elamed, Katowice.

Kahaly GJ, Dillmann WH **(2005)** Thyroid hormone action in the heart. Endocr Rev 26: 704-728.

Klein I, Danzi S **(2007)** Thyroid disease and the heart. Circulation 116: 1725-1735.

Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC **(2005)** Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 165: 2460-2466.

Stephan I, Nolte I, Hoppen HO **(2003)** The effect of hypothyroidism on cardiac function in dogs. Dtsch Tierarztl Wochenschr 110: 231-239.

Kopański R **(1984)** Rational rabbit breeding. PWRiL, Warszawa, p 207.

Pasławska U, Pasławski R, Nowak K, Płóciennik M **(2020)** The effect of hypothyroidism on the circulatory system in dogs. Wet w prakt 17: 37-42.

Pingitore A, Galli E, Barison A, Iervasi A, Scarlattini M, Nucci D, L'abbate A, Mariotti R, Iervasi G **(2008)** Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. J Clin Endocrinol Metab 93: 1351-1358.

Tilley LP, Smith FWK, Oyama M, Sleeper MM **(2010)** Cardiology of dogs and cats. ed., Edra Urban & Partner, p 269.

Ziętek J, Wilczyńska A, Jabłoński M, Sajdak S, Romanowska A, Teodorowski O, Mazurek Ł, Staniec M, Winiarczyk S, Adaszek Ł **(2021)** Clinical problems in small mammals: Eleven-year retrospective study. Med Weter 77: 95-98.