

# The Effects of Total Thyroidectomy on Cardiac Function in Old Rats using Echocardiographic Measures

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## Abstract

**Objectives:** Doppler Echocardiography has been shown to reflect thyroid hormone action in primary thyroid dysfunction. The aim of the present study was to evaluate the cardiac function after total thyroidectomy in old rats using echocardiographic measures.

**Methods:** Female Wistar rats aged 24 months old (referred to as adult) were divided into 2 groups with 15 animals each: Euthyroid (Eut) and Hypothyroid (Hypo) rats. Hypothyroidism was induced by total thyroidectomy. The plasmatic levels of T<sub>3</sub>, T<sub>4</sub>, TSH and free ionic calcium were measured. Echocardiographic analysis was performed using the following parameters: left ventricular end-diastolic (LVED) left ventricular end-systolic (LVES), ejection fraction (EF) and Tei index.

**Results:** In both groups, the LVES ranged from 0.2 to 0.5 p <0.048 and the EF from 50.3 to 45.2 p<0.030. There was not statistically significant difference in HR, LVED and Tei-index values. It was observed decrease in T<sub>3</sub> levels (72.0 to 30.4 µg/dl, p<0.001) and T<sub>4</sub> levels (3.1 to 0.4 µg/dl, p<0.001) and increase in TSH levels (1.6 to 40.7 mU/mol, p<0.001) in Hypo group. The free ionic calcium levels increased from 0.1 to 0.9 mmol/L (p<0.001) in Hypo group.

**Conclusion:** It was identified a reduction of cardiac function in old animals with hypothyroidism using Doppler-Echocardiography measures. These results indicated that hypothyroidism is associated with impairment in cardiac function in old patients and that Doppler echocardiography, is a useful and noninvasive tool for the diagnosis of cardiac dysfunction induced by this thyroid disorder.

**Keywords:** Hypothyroidism; Thyroidectomy; Doppler-Echocardiography; Old rats

## Introduction

Thyroid hormones are essential for the development of several organs and tissues and to maintenance of quality of life. They produce a general increase in carbohydrate, lipid and protein metabolism and are indirectly involved in transcriptional regulation of genes influencing all organ systems. Therefore, the clinical manifestations of their dysfunction are characteristically insidious, multiple and diverse [1-3].

Triiodothyronine (T<sub>3</sub>) and thyroxine (T<sub>4</sub>) are important thyroid hormones in regulating cardiovascular and hemodynamic function. The cardiovascular system responds to small changes in thyroid hormones levels through alterations of the vascular response and endothelial function. Hypothyroidism causes cardiomyocyte atrophy and decreased ventricular pressure and contractility [4,5]. The hemodynamic changes that characterize hypothyroidism include decrease in cardiac contractility, cardiac output, heart rate (HR) and ventricular function in general. However, the relation between thyroid hormones and aging on the cardiovascular function is controversial [2,6].

Subclinical hypothyroidism is regarded as a risk factor for the development of atherosclerosis and myocardial infarction and is associated to a diastolic dysfunction and systolic dysfunction of the left ventricle. Experimental studies have shown that thyroid disorders exert profound effects on cardiac function in rats [6,7].

Considering that hypothyroidism is one of the major endocrine diseases in adulthood and that it is associated with a significant increase in cardiovascular risk in the middle-aged. Evidence from animal and

human studies has clearly shown that aging may contribute to the development of endocrine dysfunctions such as thyroid disorders [8,9].

Because the impairment in cardiac function develops insidiously, this study was designed to investigate at which stage of evolution of the disease changes in cardiac function occur in old rats after thyroidectomy using Doppler-echocardiography measures.

## Methods

### Animal model and study design

All procedures were reviewed and approved by ethical principles in Animal Experimentation of the Brazilian College of Animal Experimentation (COBEA). The investigation using animals experiments were reviewed and approved by the Pontifícia Universidade Católica do Paraná (PUC-PR, Brazil) Institutional Animal Care and Use Committee (Approval ID 7607). Old female Wistar rats aged

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24 months old (referred to as adult) from the breeding laboratories of the “Escola de Medicina” (PUC-PR) were used throughout the study. Rats were housed two per cage under controlled humidity and temperature conditions, with an automatic 12-h light/dark cycle. Rats were randomly assigned in 2 groups: Euthyroid (Eut) and Hypothyroid (Hypo) rats. Echocardiographic analyses were performed in both groups of post-operative care. The baseline values were considered as control. Animals were fed standard rat chow from Nuvital chow (Nuvilab) and received water *ad libitum*.

### Induction of hypothyroidism

For thyroidectomy, adult rats with an average weight of 270 g were anesthetized with an *ip* injection of 50 mg/kg ketamine (Dopalen, VetBrands) + 10 mg/kg xylazine (Anasedan, VetBrands). Standard procedures were used for thyroidectomy. Briefly, a midline skin incision was made along the length of the neck. The underlying tissues were removed, and the salivary glands were retracted laterally. The two halves of the sternohyoid muscle were separated and retracted laterally. The thyroid muscle was separated from the lobes of the thyroid gland and retracted along with the sternohyoid muscle. A midline cut was made in the isthmus, and the thyroid glands were excised bilaterally. Extreme care was taken not to damage the laryngeal nerve. Sham (euthyroid/control)-operated animals underwent the same surgical procedures without removal of the thyroid gland. Rats were used for experimentation 30 and 72 days after surgery [10].

### Biochemical analysis

Establishment of altered thyroid status was confirmed by measurement of plasmatic levels of thyroid hormones ( $T_3$  and  $T_4$ ) and TSH using a competitive immunoassay (ELISA) with an enhanced chemiluminescence-end point (model Elecsys, Roche, USA). Free ionized calcium was measured by electrochemiluminescence. The results of the control group were adopted as reference values [11].

### Doppler echocardiogram

After ketamine (50 mg/kg *i.p.*) and xylazine-induced (10 mg/kg *i.p.*) anesthesia, the doppler echocardiography was performed by a single examiner using an HP Sonos 5500 transducer (Philips Medical System, Andover, MA) with 2 cm depth at 12 mHz, as in a previous report [12,13]. The echocardiographic parameters were recorded according to American Society for Echocardiography guidelines [14,15]. The echocardiographic parameters evaluated were: Heart rate (HR), left ventricular end-diastolic (LVED), left ventricular end-systolic (LVES) and ejection fraction (EF). Pulsed Doppler at the ventricular side of the mitral valve provided the flow velocity curve for analysis of diastolic function parameters such as E and A waves, E/A ratio and Tei index. The Tei index is defined as the sum of isovolumetric contraction time (IVCT) with isovolumetric relaxation time (IVRT) divided by left ventricular ejection time (ET) [16].

### Statistical analysis

All values are given as mean  $\pm$  SD. Analysis of variance (ANOVA) with repeated measurements and the LSD (Least Square difference) test for multiple comparisons were performed for comparison of the observed times (baseline, 30 and 72 days) in relation to variables that meet the condition of normalcy. For the ejection time variable, the comparison between the times was made using the Friedman non-parametric test and the Wilcoxon non-parametric test for multiple comparisons. For the Tei index, the Student’s t-test for paired samples was used. The significance level of 0.05 was corrected by the Bonferroni

method for the Wilcoxon test. All statistical analyses were performed in software version 7.0 for Windows (STATISTICA Software, USA).

### Results

There were no deaths in any of the animals included in the study. The average weight of animals ranged without significant difference between the groups over the time (data not show).

### Thyroidectomy efficacy

In order to analyze the relationship between hypothyroidisms and cardiac function in old rats, we induced a state of hypothyroidism in the animals by surgically resecting their thyroid and parathyroid glands, and then measuring the serum TSH,  $T_3$ ,  $T_4$  and free ionic calcium levels.

The thyroidectomy was effective in establish a hypothyroidic state in the animals. Table 1 shows that TSH levels were higher in Hypo group when compared with Eut group, while serum  $T_3$  and  $T_4$  levels became lower at 30 days after the surgery. Analysis of the plasmatic levels of free ionized calcium between Eut and Hypo groups did not show statistical significance ( $p=0.31$ ) throughout the experimental time period.

### Echocardiography

Doppler echocardiography, which is a well-established diagnostic tool in clinical practice, was already applied one decade ago to evaluate morphology as well as global ventricular function in rats.

Table 2 shows echocardiographic data for the Hypo group. LVED and LVES were both increased at 30 and 72 days after the surgery (table 2). There was significant decrease of EF at the same period (Figure 1). HR was similar among the 3 time-points analyzed (baseline, 30 and 72 days) in Hypo group (Table 2 and Figure 2). The difference in E/A ratios of the time-points analyzed in Hypo group was not statistically significant (Table 2 and Figure 3).

The variation in A wave in Hypo group was discrete ( $p=0.05$ ). However, post-hoc analysis by Friedman test failed to localize significative difference. Taken together with the tendency for reduced Tei index, these Doppler data suggest a progressive reduction ( $p<0.05$ ) when the baseline values are compared with the 72 days postoperatively values. The increase of Tei index (Figure 3) was associated with decreased in left ventricular ejection time (data not show).

### Discussion

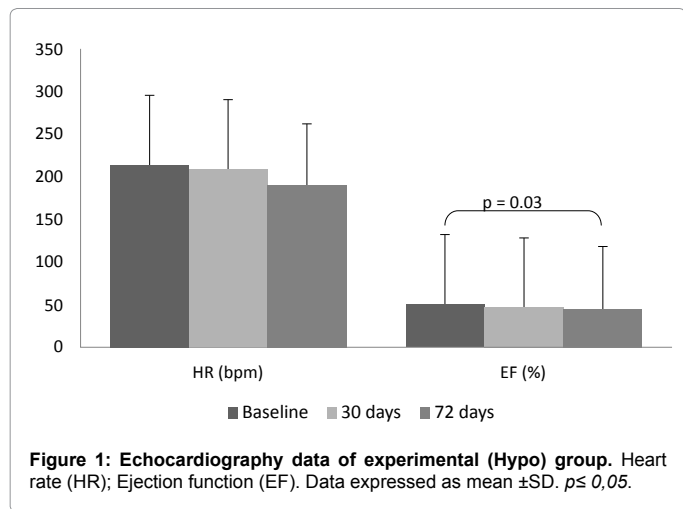
Hypothyroidism has been shown to cause low plasmatic levels of  $T_3$  and  $T_4$  and high TSH concentration [11]. Many studies reported that primary hypothyroidism is caused by elderly and that the signs and

Variables	Group	N	Mean	$\pm$ SD	P-value
TSH (mU/mol)	Eut	5	1.63	0.45	< 0.0001
	Hypo	5	40.70	9.01	
T4 ( $\mu$ g/dl)	Eut	5	3.10	0.36	< 0.0001
	Hypo	5	0.43	0.12	
T3 ( $\mu$ g/dl)	Eut	5	72.06	0.03	< 0.0001
	Hypo	5	30.49	8.02	
Ionic Calcium (mmol/L)	Eut	5	1.06	0.08	0.3150
	Hypo	5	0.99	0.13	
T3 ( $\mu$ g/dl)	Hypo	5	30.49	8.02	< 0.0001
T4 ( $\mu$ g/dl)	Hypo	5	0.43	0.12	

Table 1: Biochemical parameters of control (Eut) and experimental (Hypo) groups. Data expressed as mean  $\pm$  SD.  $p \leq 0.05$ .

Variables	Days	Mean	± SD	P-value
HR (bpm)	baseline	214	21	0.261
	30	209	26	
	72	190	51	
LVED (ml)	baseline	0.51	0.09	0.127
	30	0.52	0.12	
	72	0.59	0.08	
LVES (ml)	baseline	0.25	0.05	0.048*
	30	0.32	0.14	
	72	0.33	0.05	
EF (%)	baseline	50.3	4.52	0.03*
	30	47.2	5.63	
	72	45.2	2.66	
E (m/s)	baseline	0.66	0.13	0.254
	30	0.53	0.18	
	72	0.55	0.20	
A (m/s)	baseline	0.31	0.03	0.051
	30	0.42	0.20	
	72	0.26	0.15	
E/A ratio	baseline	2.11	0.44	0.737
	30	0.64	0.91	
	72	1.9	0.35	
Tei-index	baseline	0.49	0.08	0.544
	30	0.44	0.09	
	72	0.39	0.11	

**Table 2: Echocardiography data of experimental (Hypo) group.** Heart rate (HR); Left ventricular end-diastolic (LVED); Left ventricular end-systolic (LVES); Ejection function (EF); A wave (A); E wave (E). Data expressed as mean ± SD.  $p \leq 0.05$ .



**Figure 1: Echocardiography data of experimental (Hypo) group.** Heart rate (HR); Ejection function (EF). Data expressed as mean ± SD.  $p \leq 0,05$ .

symptoms of this endocrinal disorder are common to other diseases typical of old age, and even to the normal aging process [8,17]. In our study, serum  $T_3$  and  $T_4$  levels were significantly lower in animals submitted to thyroidectomy (Hypo group) compared to controls (Eut group) already 30 days after the surgery.

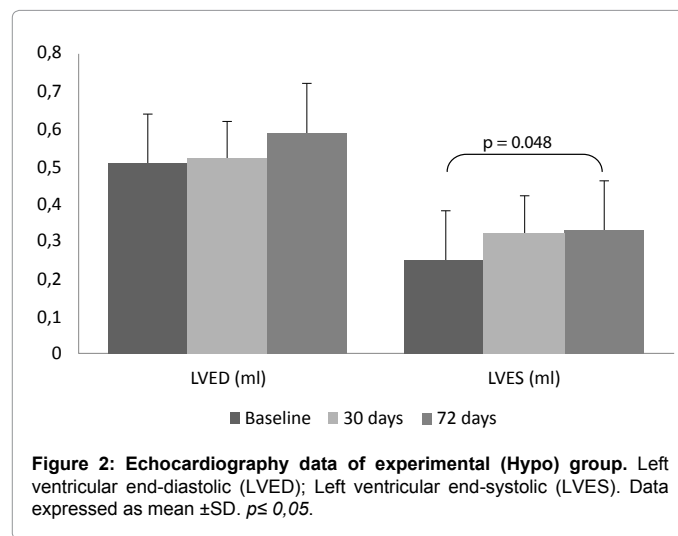
Studies have also suggested that hypothyroidism fundamentally impairs the normal functioning of left ventricle changing the myocardial inotropism and lusitropism and the systemic vascular resistance [1,9,18,19].

The most common cause of hypoparathyroidism is after thyroid surgery. Parathyroid hormone is the main parathyroid hormone which is known to act on the homeostasis of calcium and phosphate and was

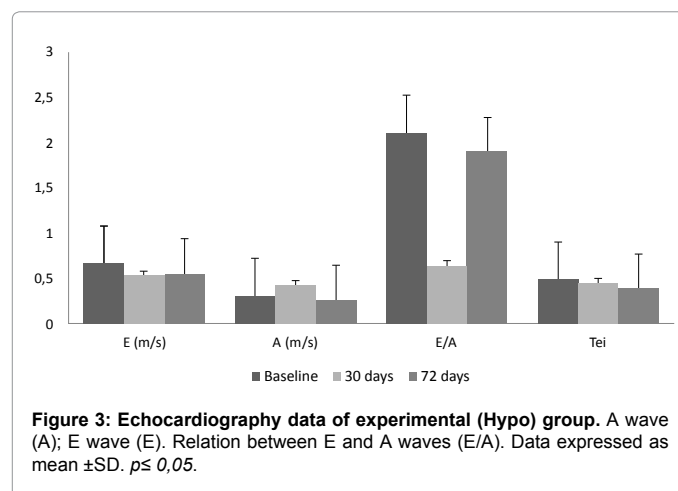
shown to have cardioprotective properties [20]. The hypocalcemia induced by hypoparathyroidism may result in bradycardia or ventricular arrhythmias, cardiovascular collapse, hypotension, decrease in myocardial contractility as well as typical electrocardiographic abnormalities [21]. In our study the both Eut and Hypo groups did not showed hypocalcemia. Therefore, all the changes in echocardiography measures in Hypo group time points (baseline, 30 and 72 days) cannot be associated with the parathyroidectomy.

Experimental hypothyroidism models are of great value to study new cardiovascular disease therapy strategies. They are easy to perform and cost effective. Nevertheless, exact monitoring of cardiac function has always been challenging due to the small size of the heart in rats. Echocardiography Doppler provides precise information, especially of myocardial function, and is an important tool for a diagnostic in clinical practice. This is particularly useful to evaluate cardiac diseases, like myocardial infarction. Moreover, therapeutic interventions, as intramyocardial stem cell injection, can be exactly monitored [3].

Reduced cronotropism, related to plasma decrease levels of thyroid hormones, has been observed in experimental studies with patients carriers of hypothyroidism [22,23]. In this study, we observed the same fact in Hypo group, with significant decrease of cardiac function at the 30<sup>th</sup> day after the thyroidectomy. As there was no significant difference



**Figure 2: Echocardiography data of experimental (Hypo) group.** Left ventricular end-diastolic (LVED); Left ventricular end-systolic (LVES). Data expressed as mean ± SD.  $p \leq 0,05$ .



**Figure 3: Echocardiography data of experimental (Hypo) group.** A wave (A); E wave (E). Relation between E and A waves (E/A). Data expressed as mean ± SD.  $p \leq 0,05$ .

in baseline HR after 30 days of the surgery, it was assumed that the impairment of heart function did not occur immediately after the thyroidectomy, but late in endocrine disorder evolution.

The HR of the animals were obtained by electrocardiographic monitoring in parallel with the echocardiographic study. It is known that the use of xylazine and ketamine are associated to a significantly altered HR [10]. In our study, all animals were submitted under the same procedure as the same dosage of drugs. Despite the drugs submission, the HR decreases naturally.

The EF fraction significantly decreased after 72 postoperative days in Hypo group. These changes were primarily due to decreased myocardial contractility and left ventricular relaxation time [12].

The thyroid hormones increase HR and EF and decrease LVES e LVED [4,24]. These findings are in accordance with our results since the Hypo group showed a slight change in HR and LVED with the positive chronotropic effect almost completely inhibited. Hypo group also showed a significative decrease of EF and increase of LVES. Hypothyroidism acts negatively on systolic contraction speed and relaxation time of heart [18]. Cardiac dysfunction caused by alteration of excitation-contraction coupling processes in rats with hypothyroidism was reported by Ogha et al. (2002). These authors reported that the speed of contraction and ventricular relaxation was significantly lower in rats with hypothyroidism [17,25]. In this study, we observed a change in myocardial contraction speed without compromise the ventricular relaxation time.

We also observed a progressive decrease of the ejection time without changes in the sum of isovolumetric time constant of relaxation. Because of these changes, there was significant decrease of Tei index. This decrease is independent of EF. Actually, the Tei Index is used as a cardiac performance parameter and predictor of cardiac impairment. It estimates the total amount of cardiac dysfunction in a simple and reproducible way apart of heart rate and blood pressure levels [26]. The values of Tei index obtained in our study support the findings in the literature about systolic, diastolic volume and ejection fraction. These results strongly suggest that thyroid hormones influence the heart function, compromising both the vascular system and the cardiac performance [27].

The mitral flow showed no change when E and A waves were compared. However, it is not possible to conclude that there was not compromise of diastolic function, such as Doppler tissue measurements were not studied.

Echocardiogram is the chosen method for determine the cardiac parameters, since it is a non-invasive procedure that allows the heart to be evaluate in details [6,22]. The Simpson method was applied in the analysis of heart function because it allows the inclusion of total ventricular cavity area, that is used for the calculation of systolic and diastolic volumes [28]. The use of echocardiography technique, in experimental animals subjected to chronic hypothyroidism, provides important information about heart dysfunction and its pathophysiology [29,30]. In our study, the final systolic volume of Hypo group at 72 days after thyroidectomy was significantly higher than the value observed at the first time point (baseline). These data demonstrate that animals with hypothyroidism have reduced myocardial contractility; promoting reduction of systolic flow in a time-dependent relationship. It was not observed significant changes in cardiac function at 30 days after thyroidectomy. However, at 72 days after the surgery, it was detected a significant increase in LVES and a decrease in EF. According to the findings in the literature, the EF values established in this study were

significantly lower. The decrease in EF may represent the real cardiac functional events in old rats, as reported by Biondi and Kein (2004). These authors showed the influence of thyroid hormone on heart rate, systolic, diastolic function and total peripheral vascular resistance [18].

Although not statistical significative, the values of HR showed a tendency to reduction when all the time points (baseline, 30 and 72 days) are taken together. On the other hand, the significative lowering of EF induces the concomitant decrease in overall cardiac output. The effect of thyroid hormones on hemodynamic variables, such as heart rate (HR), cardiac output, pre and post load components, systolic pressure, diastolic pressure and pulse pressure, is a result of higher or lower peripheral metabolic demand associated with hyperthyroid or hypothyroid states, respectively [31].

The heart and kidney are very closely related. Thus, derangement of cardiac function can induce renal dysfunction, recently referred to as “cardiorenal syndrome (CRS)” or inversely as “renocardiac syndrome”. CRS can be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other [32].

Studies have also detected associations between low cardiac output and cognitive and neuroimaging abnormalities and it is also plausible that lower cardiac output could be a risk factor for abnormal brain aging and dementia [33]. Other studies demonstrate the effects of thyroid disorders on cardiovascular and muscle systems, impairing cardiac function and decreasing the ability to perform daily activities, because of exercise intolerance [34].

Therefore, hypothyroidism and aging induce changes in the cardiac function and, consequently, deterioration of many systemic and physiological functions. Furthermore, there is increasing evidences from observational studies for an association between hypothyroidism and the risk of cardiovascular disease-related morbidity and mortality [35].

## Conclusion

The recognition of correlations among aging processes, hypothyroidism and changes occurring in the myocardium has refocused new researches on the pathophysiology of cardiac disease.

There are several studies employing animal models that demonstrate the consequences of thyroid disorders on the cardiovascular system, with impaired cardiac function as one of the main consequences.

To our knowledge, this is the first study that characterizes the loss of systolic function of the left ventricle in thyroidectomized old rats through echocardiographic examination.

New studies should be encouraged for the purpose of assessing variations in the secondary disorders of thyroid function and their implications, as well as therapeutic possibilities for this very prevalent disease.

## Declaration

The authors declare no conflict of interest in this study.

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