

## ORIGINAL ARTICLE

## Effects of Hyperthyroidism on Contractility and Na<sup>+</sup>/Ca<sup>2+</sup> Exchanger Activity in the Isolated Papillary Muscle of Rats

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### Abstract

**Background:** Hyperthyroidism (Hy) is an endocrine disorder, in which the thyroid hormones markedly alter the cardiac function. Increased myocardial contractility and cardiac output, improvement in diastolic relaxation, changes in electrical activity, increments in ventricular mass, and arrhythmias have been reported. However, the influences of thyroid hormones upon molecular mechanisms of cardiac functions have not yet been fully understood.

**Objectives:** To evaluate changes in cardiac contractile parameters and the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX) function in induced hyperthyroid rats.

**Methods:** Hy was induced by intraperitoneal injections of T3 (15 µg/100 g) for 10 days. Contractile parameters and NCX function were evaluated in the isolated papillary muscle. Data normality was confirmed by the Shapiro-Wilk test. The comparison between groups was performed through an unpaired Student's t-test. Results are expressed as mean ± SD. The accepted significance level was  $p < 0.05$ .

**Results:** Our data revealed, in the Hy group, an increase of 30.98% in the maximum speed of diastolic relaxation ( $-284.64 \pm 70.70$  vs.  $-217.31 \pm 40.30$  mN/mm<sup>2</sup>/sec ( $p = 0.027$ )) and a boost of 149% in the NCX function in late phase of relaxation ( $20.17 \pm 7.90$  vs.  $50.22 \pm 11.94$  minutes ( $p = 0.002$ )), with no changes in the maximum twitch force ( $p = 0.605$ ) or maximum speed of systolic contraction ( $p = 0.208$ ) when compared to the control.

**Conclusion:** The improvement in relaxation parameters is hypothetically attributed to an increase in Sarco-Endoplasmic Reticulum Ca<sup>2+</sup>ATPase isoform 2 (SERCA2) expression and an increased calcium flow through L-type channels that boosted the NCX function.

**Keywords:** Hyperthyroidism; Thyroid Hormones; Papillary Muscles; Rats; Sodium-Calcium Exchanger; Myocardial Contraction.

### Introduction

The thyroid hormones (TH) play a role in the entire organism, regulating biological processes, such as metabolic rate, oxygen consumption, gene transcription, and protein synthesis.<sup>1,2</sup> Hyperthyroidism (Hy) is characterized by an increase in the endogenous production of the triiodothyronine (T3) and/or thyroxine (T4) hormones, or by the exogenous administration of these hormones.<sup>3</sup> The heart is the major target organ for TH actions.<sup>4,5</sup>

In the heart, TH has an effect on the membrane ion channels,<sup>6</sup> on the contractile apparatus, and on the sarcoplasmic reticulum (SR),<sup>7</sup> which are linked to the excitation-contraction coupling mechanism<sup>8</sup> and directly alter contractility.<sup>9</sup>

Common changes reported in the hyperthyroid heart are increased myocardial contractility and cardiac output,<sup>2</sup> improvement in diastolic relaxation,<sup>10</sup> changes in electrical activity,<sup>7</sup> increments in ventricular mass,<sup>5</sup> and arrhythmias.<sup>1</sup>

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In short-term Hy, TH is a positive regulator of the cardiac function. By contrast, in the long-term, TH promotes deleterious effects in the heart,<sup>5</sup> causing heart problems, the major cause of death in hyperthyroid patients.<sup>6</sup> However, the influences of TH in molecular mechanisms of the cardiac function have not yet been fully understood. Thus, the present study aimed to evaluate functional changes in contractile parameters and the Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX) function in the isolated papillary muscle 10 days after hyperthyroidism had been induced in rats. This investigation could bring new evidence to explain the actions of TH in the physiology of the heart.

## Methods

### Animals

Thirty-two male Wistar rats, weighing 250-300 g were provided by the Experimental Animal Center of the Federal University of Paraná. The animals were kept in cages under controlled conditions of temperature and a light-dark cycle of 12 h, with free access to food and water. All experimental protocols used in this study were approved by the Animal Experimentation Ethics Committee of the Biological Sciences at the Federal University of Paraná (license number: AECC-747) and conducted in accordance with the National Council of Animal Experimentation (CONCEA) guidelines. Rats were randomly divided into the control group (CG, n=16) and the hyperthyroidism group (HG, n=16). Hy was induced by intraperitoneal injections of T3 (15 µg/100 g) for 10 days. The CG received daily injections of saline solution during the same period.<sup>11</sup> The sample size was calculated based on the following statistical criteria:  $r=2t\alpha^2s^2/d^2$ , where  $r$  is the sample size,  $s^2$  is an estimate of the experimental variance from previously performed experiments;  $t\alpha$  is the  $t$  value with the  $s^2$  degrees of freedom for the  $\alpha$  level of probability;  $d$  is the desired difference between treatments. The sample size for each group was calculated as follows:  $r=s^2q^2F/d^2$ , where  $s$  and  $d$  were defined in the equation above, and  $F$  is the  $F$  value for the  $\alpha$  level of probability with  $\gamma_1$  and  $\gamma_2$  degrees of freedom from performed experiments, and  $q$  is the studentized range for the experiment to be performed. The  $q$  value is the same as that obtained by the Tukey's test table for the  $\alpha$  significance level.<sup>12,13</sup> The randomization was performed on the following website: Randomization.com ([www.randomization.com](http://www.randomization.com)).

### General Protocol

After the treatment, the animals were weighed, anesthetized with an intraperitoneal injection of ketamine (50 mg kg<sup>-1</sup>) and xylazine (20 mg kg<sup>-1</sup>), and euthanized by exsanguination. The chests were opened, the hearts collected and quickly transferred to a Becker containing Ringer's solution (RN) in order to remove the blood from cardiac cavities. This solution had the following composition (in mM): NaCl = 110, KCl = 4, CaCl<sub>2</sub> = 2, MgCl<sub>2</sub> = 2, TRIZMA = 10 and glucose = 11, pH adjusted to 7.4 with NaOH or HCl. In sequence, the hearts were weighted and fixed in a Petri dish containing RN for papillary muscle dissection, performed as previously described by Szkudlarek et al.<sup>14</sup>

The myocardial portion was fixed to a micromanipulator while the tendinous portion was attached to a force transducer (Fort 10 WPI, Transduction Laboratories Co.), which was calibrated before each experiment using known masses. The muscles were then transferred to a 3 ml chamber containing RN at 30C°, continuously gassed with pure oxygen. This chamber was built in a mobile acrylic block allowing for the transfer of the muscle from one chamber to another, exposing it to the desired composition solutions.

To evaluate the effects of Hy on the heart, papillary contractility was assessed in two protocols. In the first, twitch measurements, such as maximum isometric twitch force (Tmax), maximum speed of force development (+dF/dt), maximum speed of force decrease (-dF/dt), and maximum force (Fmax) in response to increasing caffeine concentration (0.5, 3, 10 and 30 mM), were evaluated. In the second, the NCX contribution to muscle relaxation was evaluated. After each experiment, the muscle length was measured with a graticule positioned at the eyepiece of a microscope. The cross-sectional area (CSA) was calculated using the formula:  $A=\pi r^2$ . Tmax, +dF/dt, -dF/dt, and Fmax were normalized by the CSA muscle and are expressed in milliNewton per square millimeter (mN/mm<sup>2</sup>). The data were collected using an acquisition system PowerLab 4/30, (AD Instrument) and subsequently analyzed using Lab Chart version 7.3.7 software.

### Protocol 1

The isolated papillary muscles attached to the force transducer were stimulated (1 Hz) with supra-threshold voltage pulses (15 V) with a duration of 5 milliseconds through a pair of platinum electrodes positioned along the entire length of the muscle. The muscles were stretched

to the length where the maximum active tension ( $L_{max}$ ) was obtained. Under these conditions, the muscles were maintained for a stabilization period of 30 minutes. The twitch measurements ( $T_{max}$ ,  $+dF/dt$ ,  $-dF/dt$ ) were then analyzed for 10 minutes of stable contraction.

After the twitch measurements, papillary muscles were quickly transferred to a chamber containing zero sodium and zero calcium Ringer's solution (R0) for 15 minutes to block the NCX<sup>15</sup>. In R0 solution, sodium and calcium ions were replaced with lithium chloride (LiCl) to maintain equal levels of osmolarity and ionic strength, as seen in RN. In sequence, the muscles were transferred to a chamber containing R0 + 0.5 mM caffeine. After reaching the maximum force ( $F_{max}$ ) in a plateau, the muscle was transferred back to the R0 chamber until complete relaxation. The process was then repeated with 3, 10, and 30 mM of caffeine.

## Protocol 2

As described above, the muscles were electrically stimulated for a stabilization period of 30 minutes. In sequence, the electrical stimulation was stopped, and the papillary muscle was transferred to a chamber containing R0 + 10  $\mu$ M of cyclopiazonic acid for 15 minutes in order to block SR  $Ca^{2+}$  uptake by Sarco-Endoplasmic Reticulum  $Ca^{2+}$  ATPase isoform 2 (SERCA2).<sup>16</sup> The muscle was then transferred to a chamber containing R0 + 30 mM of caffeine. After reaching  $F_{max}$  in a plateau, the muscle was transferred to a chamber containing RN, unblocking the NCX. In this condition, with the SR  $Ca^{2+}$  pump blocked, the NCX contribution was evaluated by the muscle relaxation time for early and late phases of muscle relaxation.

## Statistical analysis

Results are expressed as mean  $\pm$  SD. The Shapiro-Wilk test was used to test data normality. For comparisons

between groups, an unpaired Student's t-test was used. For data analysis and plotting, Graph Pad Prism 5 (Graph Pad Software, San Diego, California, USA) was used. The accepted significance level was  $p < 0.05$ .

## Results

Body and heart weight of all animals after 10 days of treatment are represented in Table 1. As expected in HG, body weight decreased 7.35%, and heart weight increased by 18.98% when compared to CG.

### Twitch measurements

$T_{max}$  and  $+dF/dt$  did not differ between groups. However,  $-dF/dt$  significantly increased 30.98% in HG (Table 2).

### $F_{max}$

As represented in Table 3, the maximum force in response to increasing caffeine concentration did not differ between groups.

### NCX assessment for relaxation

After reaching the contraction plateau at 30 mM of caffeine, the early and late phases of muscle relaxation were analyzed. The early phase did not differ between groups. The late phase significantly declined (149%) in HG (Table 4).

## Discussion

In this study, contractility in isolated papillary muscles from induced hyperthyroid rats was assessed and demonstrated an increase in the speed of diastolic relaxation ( $-dF/dt$ ) associated with a higher NCX function when compared to the CG. No changes were observed in contractile force ( $T_{max}$  and  $F_{max}$ ) or in maximum speed of systolic contraction ( $+dF/dt$ ).

**Table 1 – Body and heart weight**

	Body weight	Heart weight
CG	297.80 $\pm$ 12.75	1.11 $\pm$ 0.07
HG	277.44 $\pm$ 17.78	1.37 $\pm$ 0.17
p-value	0.010	<0.001

Values are expressed in grams. Data is expressed as mean  $\pm$  SD. Control Group (CG, n=16) and Hyperthyroid Group (HG, n=16).

**Table 2 – Twitch measurements**

	Tmax	+dF/dt	-dF/dt
CG	27.76 ± 4.53	263.80 ± 47.17	-217.31 ± 40.30
HG	26.64 ± 4.38	297.91 ± 59.66	-284.64 ± 70.70
p-value	0.605	0.208	0.027

Maximum isometric twitch force (Tmax) is expressed in mN/mm<sup>2</sup>. Maximum speed of contraction (+dF/dt) and maximum speed of relaxation (-dF/dt) are expressed in mN/mm<sup>2</sup>/sec. Data is expressed as mean ± SD. Control Group (CG, n=8) and Hyperthyroid Group (HG, n=8).

**Table 3 – Fmax in response to increasing caffeine concentration**

	0.5mM	3mM	10mM	30mM
CG	1.25 ± 0.31	2.56 ± 1.63	2.62 ± 1.56	3.05 ± 1.67
HG	0.88 ± 0.44	1.60 ± 1.13	1.55 ± 1.15	1.98 ± 1.03
p-value	0.178	0.251	0.276	0.239

Maximum force (Fmax) is expressed in mN/mm<sup>2</sup>. Data is expressed as mean ± SD. Control Group (CG, n=8) and Hyperthyroid Group (HG, n=8).

**Table 4 Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCX) contribution for muscle relaxation**

	early phase	late phase
CG	39.40 ± 22.17	50.22 ± 11.94
HG	33.80 ± 29.06	20.17 ± 7.90
p-value	0.741	0.002

Early phase is expressed in seconds. Late phase is expressed in minutes. Data is expressed as mean ± SD. Control Group (CG, n=8) and Hyperthyroid Group (HG, n=8).

In animals treated with T3, an increase in the cardiac mass/body mass ratio is commonly reported.<sup>1,5,14,17</sup> This was also observed in this study. Such results are related to a rise in the basal metabolic rate, increased energy expenditure, and oxygen consumption associated with an increment in protein and lipid catabolism.<sup>10,18</sup> In cardiac myocytes, an increase in total protein synthesis<sup>9</sup> and an incremented expression of the alpha myosin heavy chain ( $\alpha$ -MHC)<sup>6</sup> were observed, which resulted in an enhanced myocardial function.<sup>2</sup>

The papillary muscles of hyperthyroid rats showed no changes in contractile force when compared with the controls (Tmax, Table 2), which runs in line with results obtained by Szkudlarek et al.<sup>14</sup> and Vieira et

al.<sup>11</sup> Fmax in response to caffeine (Table 3) also showed no differences, which demonstrated that the SR Ca<sup>2+</sup> content has not changed, which is in agreement with previous data published by Alba-Aguayo et al.<sup>1</sup>

Regarding contractility, represented by +dF/dt and -dF/dt, the available information is conflicting, and there is paucity of data. Our data revealed no changes in +dF/dt and a significant increase in diastolic function in HG when compared to the CG (Table 2); similar results were observed by Szkudlarek et al.<sup>14</sup> and Palmieri et al.<sup>19</sup> Vieira et al.<sup>11</sup> reported an increment in + and -dF/dt and a decrease in time to peak contraction. On the contrary, Wolska et al.<sup>8</sup> reported an increase in time to peak contraction, while

Rozanski et al.<sup>5</sup> reported a decrease in  $+dF/dt$  and no changes in  $-dF/dt$ .

Szkudlarek et al.<sup>14</sup> showed, *in vivo*, the effects of Hy in rats using echocardiography, and, in HG, demonstrated a decreased end diastolic volume, a total diastolic time and ejection time associated with the increased heart rate, an ejection fraction, and a cardiac output. In a similar experiment, Palmieri et al.<sup>19</sup> observed in hyperthyroid patients that the increased left ventricle performance was sustained by increased preload with enhanced diastolic function.

The changes in cardiac function promoted by Hy are commonly associated with the upregulation of ryanodine receptors isoform 2 (RyR2)<sup>17,20,21</sup> and SERCA2 expression,<sup>7,9,10</sup> as well as the downregulation of phospholamban (PLB).<sup>1,6,7</sup> Moreover, TH stimulates the expression of  $\beta$ -adrenergic receptors in the heart,<sup>6,8,9</sup> which raises the sensitivity to sympathetic stimulation. The activation of the AMPc/PKA/CaMKII pathway leads to increments in RyR2 and PLB phosphorylation with a consequent rise in the  $Ca^{2+}$  release to sarcoplasm and the  $Ca^{2+}$  uptake to SR.<sup>22</sup>

For the diastole,  $Ca^{2+}$  is removed from the cytosol by four mechanisms: SERCA2, NCX, the plasma membrane  $Ca^{2+}$ ATPase (PMCA), and the mitochondrial  $Ca^{2+}$  uniporter.<sup>22</sup> In rat ventricles, under normal conditions, approximately 92% of cytosolic  $Ca^{2+}$  is removed by SERCA2, 7% by NCX, and 1% by PMCA and  $Ca^{2+}$  uniporter.<sup>23</sup> The NCX activity assessment, represented in Table 4, revealed no changes in the early phase of relaxation between the groups. However, a significant decline of 149% in the time of late-phase relaxation was observed in the HG when compared to the CG. Although there is a record of increment,<sup>24</sup> most papers report a decline in NCX expression in Hy.<sup>2,25</sup> Cernohorský et al.<sup>26</sup> showed a 50% reduction in rat ventricular NCX expression. According to Davis & Davis,<sup>27</sup> the PMCA appears to be indirectly influenced by TH through increased PKC activation, although its function is unlikely to influence cytosolic  $Ca^{2+}$  concentration.

Another mechanism by which T3 alters the cardiac function is by modulating the activity of  $Ca^{2+}$  channels in the cell membrane.<sup>2</sup> Gotzsche<sup>28</sup> attributes the changes in myocardial  $Ca^{2+}$  homeostasis to an augmented expression of the  $\beta$ -receptor and the activity of AMPc/PKA/CaMKII pathways, while Yu et al.<sup>29</sup> reports an increased activity of these pathways

with increased L-type  $Ca^{2+}$  channel phosphorylation, raising the density of  $Ca^{2+}$  currents through these channels. According to Bers,<sup>22</sup> the  $Ca^{2+}$  that enters via ICa is approximately the same as that extruded by the NCX. A consequence of the increased  $Ca^{2+}$  entry in the cell is an increased  $Ca^{2+}$  extrusion via NCX, which may have boosted the exchanger activity.

In this work, after the contraction of the papillary muscle had been induced by caffeine in the presence of cyclopiazonic acid, simultaneously with the reactivation of NCX, the late phase of relaxation was reduced. Since in this condition the activity of the SR  $Ca^{2+}$  pump was blocked, the relaxation of the muscle was mainly due to NCX activity. This suggests that Hy induced an increase in activity and/or expression of NCX.

## Conclusion

Much information is missing concerning hyperthyroidism and the cardiac function, especially in isolated muscles. Certainly, the time at which the cardiac muscle is exposed to an increase in circulating thyroid hormones influences the magnitude of the consequences, whose primary changes seem to be related to an increase in the cardiac mass/body mass ratio and increased relaxation kinetics.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This article is part of the thesis of master submitted by Angela Mara Rambo, from *Universidade Federal do Paraná*.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee on Animal Experiments of the *Universidade Federal do Paraná* under the protocol number CEEA-747.

## Author contributions

Conception and design of the research: Fogaça R, Rambo A. Acquisition of data: Rambo A, Silva I. Analysis

and interpretation of the data: Rambo A, Peixoto J, Albuquerque R. Statistical analysis: Peixoto J. Writing of the manuscript: Rambo A, Peixoto J. Critical revision of the manuscript: Fogaça R, Silva I, Albuquerque R.

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