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Cardiac Activity Assessed *in vivo* and *in Vitro* in Rats Treated with Propiltiouracil (PTU)

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Abstract— *Thyroid hormones interfere with cardiovascular functions causing morphofunctional changes in cardiomyocytes, evidenced by electrophysiological activities and hemodynamics. This study examined the implications of hypothyroidism on cardiac electrical activity in Wistar rats under experimental conditions in vivo and in vitro. It was approved by the animal ethics committee (CEUA-University of Gurupi-TO, Brazil), using 20 rats (male and / or female), randomly subdivided into 10 control rats (treated with water + aspartame) and 10 experimental rats (treated with water + aspartame + PTU) for 4 weeks. On the 31st day, in thestudies in vivo, the electrocardiographic tracings (ECG DL 660 Delta Life) were obtained with the anesthetized animals and, in the Langendorff preparation, the hearts were isolated and perfused in a chamber with electrodes (Ag / AgCl) connected to the ECG and recorded cardiac electrophysiological activity. In both protocols the analyzed variables were: heart rate (BPM), amplitudes (mV) of P, QRS and T deflections and intervals (ms) PR, QRS and QT. The results obtained were bradycardia, prolongation of the PR interval, QRS and QT interval in bothprotocols in vivoin and in vitro rats treated with Propylthiouracil (PTU). In theexperiment in vitro there was a reduction of P wave amplitude and no significant change in ventricular contractility compared to the control group. It is concluded that the deficit of thyroid hormones alters the functions of cardiac chronotropism and dromotropism evidenced by bradycardia and stretching of PR, QT and QRS intervals.*

Keywords— Hypothyroidism. Cardiac Evaluation. Langendorff. Propylthiouracil. Epidemiology.

I. INTRODUCTION

Cardiovascular physiology, as well as cardiology, has advanced in the treatment of cardiovascular dysfunction as a result of basic experimental and clinical research with animals in the last five decades of what has occurred over two centuries.

The electrocardiogram (ECG) identifies the structural and hydroelectrolytic changes of cardiomyocytes associated with changes in the amplitudes and duration of cardiac action potential (PAC) demonstrated by the behavior of the electrophysiological waves of the heart, being of use in both animal and human experiments, consisting of a non-invasive examination and capable of ensuring good quality research with reliable results [1]. (CHRISTOFOLETTI et al., 2013).

Cardiovascular dysfunctions, associated with shorter life expectancy, are a growing public health problem becoming the target of research in experimental animal models and replications in humans [2]. (Graes and Swers, 2014). Is a challenge for epidemiology in health,

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seen growing prevalence such disorders in the world's population.

The thyroid glands produce the hormones T_4 and T_3 and basically perform functions on the metabolism of the human body in order to increase it [3]. (GONÇALVES et al., 2006). Thyroid dysfunction affects thousands of people worldwide, and it is relevant to understand how this dysfunction interferes with cardiac electrical activity [4]. (1998). Changes in the number of hormones produced by the thyroid gland, particularly thyroxine modifies cardiac activity by different means: 1) T_4 acts directly on myocyte through nuclear receptors which in turn will act on genes, 2) T_4 mediates a non-nuclear mechanism, 3) through the change in vulnerability and nervous system tone in the sympathetic system, and finally 4) the T_4 causes an increase in energy consumption, resulting in a greater capacity of muscular contraction [5]. (THOMAL, 2007).

The deficit of HT or hypothyroidism is also dysfunction thyroid and can lead to changes in heart electrical activity, evidenced by changes in cardiac inotropic and chronotropismthe [6]. (NASCENT, 2011). In this diagnosis, the gland does not synthesize T_3 and T_4 or only with high TSH levels [7,8]. (Edwards et al., 1991).

For a better understanding of the action of HT on cardiac activity, it is necessary to know the electrocardiographic profile, and the studies may occur in adult rats since they are stable in this phase of life, serving as parameters for the identification of ECG tracing changes in rats with disorders of thyroid hormones [1]. (CHRISTOFOLETTI et al., 2013). In the ECG, imbalances in the sodium or potassium channels, metabolic disorders or electrical changes due to anatomical and physiological abnormalities, affect the amplitude, duration and/or intervals between electrophysiological waves, exacerbating, among the main functional modifications, chronotropic and or cardiac inotropism [9]. (ZORNOFF et al., 2009). The normal profile of the electrocardiographic waves in studies with rats is expressed in the complete order of the P, Q, R, S, and T waves, in which a significant oscillation in the S wave voltage and signs of the absence of the P wave can be observed [1]. (CHRISTOFOLETTI et al., 2013).

Propylthiouracil (PTU) is a drug prescribed for the treatment of hyperthyroidism in humans and, in animal models generally with rodents, has been used to induce in these the clinical picture of hypothyroidism. Data from animal modeling to verify the effect of thyroid hormones (HT) on myocyte gene expression has been supported for clinical studies in humans [10]. (HAJJE et al., 2014). Morphological and structural changes observed in cardiomyocytes caused by the absence of HT in rats induced hypothyroidism by ingestion of PTU evidenced heart failure by reduction of myocardial blood flow associated with a decrease in the number of arterioles [11,12]. (TANG et al., 2005 apud CHENG et al., 2012). Propylthiouracil (PTU) reduces the peripheral conversion of $T_4$to $T_3$by inhibiting the Type 1 (D 1) deiodinase present in peripheral tissues and in the thyroid. High doses of PTU have a beneficial action when a faster control of the thyrotoxicosis is desired [13,14]. (Andrade, 2001; Lopes, Vale, Ogawa, 2016).

In hypothyroidism, changes observed on the ECG are generally characterized by bradycardia, reduced P wave amplitude, low QRS complex voltage, attenuation or inversion of the T wave, prolongation of the PR, QRS and QT intervals and, uncommonly, a ventricular tachyarrhythmia [15,16,17]. (Vorges-Uricoechea et al., 2004).

Cardiovascular diseases are the leading causes of mortality and morbidity worldwide. The heart is among the organs most responsive to the action of thyroid hormones, which, under the clinical manifestations of hypothyroidism and human evolution, may present a reduction in heart rate, decreases in contractility, speed of myocardial relaxation, decrease in return increased peripheral vascular resistance.

For this reason, the objective of this study was to evaluate the cardiac performance of hypothyroid Wistar rats induced by the administration of PTU under experimental conditions *in vivo* and *in vitro*, providing valuable information about the cardiovascular pathophysiology caused by this thyroid dysfunction. alterations in electrophysiological parameters. In this study, the Langendorff perfusion method was used to isolate the rat heart for the purpose of the study. This experiment was pioneered in the state of the Tocantins, Brazil, which extends the possibilities of its application to this type of scientific investigation.

This Langendorff method resulted from a slow-paced discovery that lasted more than a hundred years. However, it has the advantage of providing computerized data acquisition, followed by storage and processing to increase electrophysiological and hemodynamic knowledge [18]. (BELL et al., 2011). Several laboratory tests are performed worldwide based on Langendorff's methodology, including technical improvement for new discoveries such as metabolism and coronary regulation studies using conventional chemical methods and magnetic resonance and Doppler echocardiography techniques [19]. (SKRZYPIEC-SPRING et al., 2007).

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II. MATERIALS AND METHOD

2.1. Type of study, site, sample, ethical principles

An experiment was carried out using animal modeling of Wistar rats from the laboratory of the Universidade de Gurupi - UnirG, State of Tocantins, Brazil. All treatment, manipulation and euthanasia procedures were carried out in strict compliance with the resolutions of the specific Brazilian Bioethics standards in Experiments with Animals, Law Procedures for the Scientific Use of Animals, N^0 11794 - sanctioned on October 8, 2008 - National Council for Control of Animal Experimentation - CONCEA. This research was approved by the Ethical Committee on the Use of Animals (CEUA) of UnirG University, protocol nº 06/2018.

All the experiments were elaborated, delineated, conducted and carried out in the Laboratory of Physiology of Campus 2, UnirG. Twenty *Wistar* rats (male and/or female) supplied by the clinic's normal central laboratory, fed with standard feed Nuvilab and water *ad libitum, were used*. The animals were kept for at least seven days in the new environment, for the purpose of setting and housed in polypropylene boxes with dimensions 41 x 34 x 16 cm, lined with dry rice straw, in a number of five per box, in an environment with temperature monitored around 25ºC.

For control of the circadian rhythm, they were kept in the room with light / dark cycles of twelve hours. The level of the noise intensity of the site is, on average, 54.7 dBA, previously measured by means of a digital decibel meter (IMPAC model IP-130), below the noise considered stressor for these animals. Storage boxes were sanitized three times a week. Throughout the experiment, it was evaluated daily by visual inspection on clinical aspects such as mobility, body weight, water and food intake, eye coloring, degree of coat, behavior, possible wounds, etc. The balance used for weighing the animals is electronic with a scale of up to 7 kg with an accuracy of 1 gram (CE mark, model SF-400). The criteria for inclusion of the animal sample were: 20 Wistar rats (males and/or females), clinically healthy, around three months of age, the weight of 250-500 g, good mobility and normal coat. Although the animals were kept in boxes by gender, this fact was not considered during the data collection, because, in the bibliography, no consensus was found on the influence of gender on electrocardiographic tracings. Obese animals have excluded females in offspring, older than three and a half months of age and with suspected clinical status, avoiding possible biases in the result due to the interference of such factors.

2.2. Design and procedures

The rats were divided randomly and gender into two groups identified in boxes: control (ten mice, five males in a box and five females another) and OCT (ten mice, five males in a box and five females other) [20]. (TOHEI et al., 1998).

Propiltiouracil® (PTU, BIOLAB), a drug used to treat hyperthyroidism and used as an inducer of hypothyroidism in laboratory animals, acts by inhibiting the synthesis of HT and the peripheral conversion of T_4 to T_3, was prepared daily and administered in the amount of 1 mg / mL in the drinking water for 30 days [21]. (FERREIRA et al., 2007).

To overcome the drug-aversive behavior, aspartame PTU was added in the concentration of 10 drops / 100 mL of water, which reduces such behavior. For the animals in the control group only water was supplied, but containing aspartame in the same concentration as that used in the PTU group, in order to reduce the bias by administering the sweetener in only one of the groups. Its mechanism of action is to inhibit the synthesis of thyroid hormones by interfering with the use of intrathyroid iodide (iodine) and the coupling reaction between iodide and tyrosine residues, resulting in iodine disorganization. This mechanism, in turn, results in enlargement of the thyroid gland which is one of the clinical signs of hypothyroidism [22,23]. (MAIA et al., 2013, NELSON, COUTO, 2015).

In rats treated with PTU, blocking of iodine metabolism occurs, leading to an increase in the concentration of iodide observed by the enlargement of the thyroid gland. Inhibition of enzymes specific for deiodases leads to hypothyroidism and an increase in TSH leads to hypertrophy and hyperplasia of the thyroid epithelium and an increase in the concentration of iodide leads to an increase in the volume of the gland [24,25,26]. MOURA; PAZOS DE MOURA, 2004; ANTONIADIS et al., 2003; NUNES, 2003).

In the experimental model of induction hypothyroidism with PTU, the findings of several studies show predominant clinical signs such as reduction of heart and body weight, reduction of hair quality with falls and bruising, reduction of water intake and increase of the volume of the thyroid gland are the signs of the presence of HT deficits [27,12,28,29,30]. (Hahn et al., 2005), and the results obtained in this study are presented in Table 1.

The electrophysiological changes of the cardiac activity in an experimental model of hypothyroidism by ingestion of PTU are confirmed by the evaluation of the ECG profile with significant changes in chronotropism, inotropism, and cardiac dromotropism being a predictor of the thyroid dysfunction signal [31,32,30]. (Engelha et al., 2005).

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The diagnosis of hypothyroidism is based on the clinical manifestations associated with the laboratory results through analysis of the reduction T_3, T_4 and increase of TSH or HRT, techniques out of reach in the Laboratory of Physiology of UnirG. Therefore, all mention of PTU-treated rats will be assumptions of being hypothyroid [23]. (NELSON; COUTO, 2015).

After euthanasia, the thyroids were dissected by tracheal cervicotomy, exposed and photographed to assess the volume dimension compared to control animals, thus subsidizing the diagnosis of hypothyroidism (Figure 1).

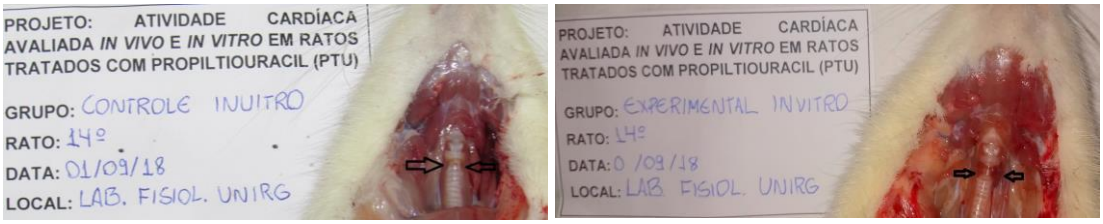

Fig.1: Ectoparasitic rat tracheal cervicotomy (Control group) and signs of thyroid gland hypertrophy (Experimental grou p). UNIRG of Physiology Laboratory, Gurupi-TO, Brazil, 2018.

In the description of the Langendorff apparatus (Figure 2) accommodating the camera and the isolated heart perfused by Krebs-Ringer Henseleit solution is acrylic material, robust, with dimensions 20 cm height x 8 cm wide x 12 cm deep. It has four holes through which the Ag / AgCl electrodes pass and another cannulated orifice located in the back (not shown in the figure) where the excess liquid was collected by gravity and scorned in a 2000 mL capacity plastic collection bag positioned in the bottom of the workbench. The temperature gradient of the perfusion solution was on average around 2 ° C, because in the vessel the thermostat was calibrated to about 39 ° C reaching the solution that perfused the heart around 37 ° C. The aeration of the solution moved by atmospheric air pressure occurred by means of an aquarium pump endowed at its end by a porous material and, when immersed in the Krebs-Henseleit Ringer, provided a vigorous ablation.

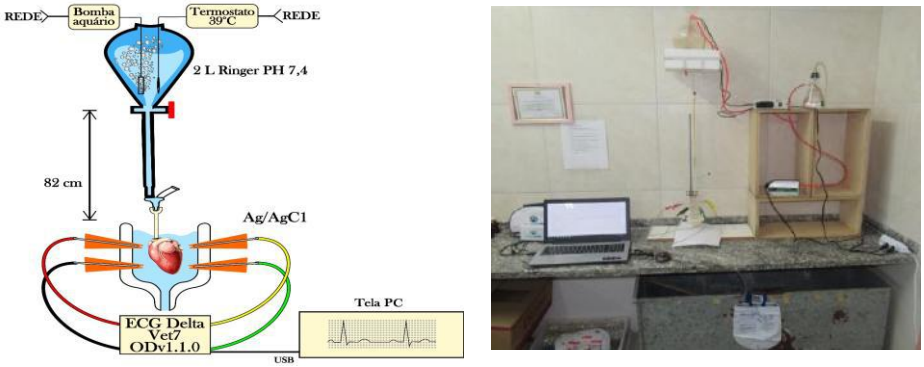

Fig.2 - Langendorff system used to study heart in vitro of control and PTU treated rats. Source: Authors, 2018.

These experimental conditions allowed to conduct studies *in vitro* at a time interval of up to 30 minutes, a period that was enough to obtain ECG records with relative stability. The height of 82 cm equals 60 mmHg within the established standard. A cannula inserted and tethered in the ascending aorta allowed the heart to be positioned vertically. The container fixed to the wall containing solution at a height of 82 cm by gravity perfused the heart, the perfusion flow being regulated by a part provided by an opening/closing mechanism which may enable, in future projects, inputs for drugs and agonist substances or antagonists. Ag / AgCl electrodes were connected to ECG DL 660 (Delta Life), two of them in the atria and two in the ventricles, with the objective of evaluating cardiac work under the inotropic and chronotropic aspects. An acrylic bottle containing the heart was used with the cannula of fixation in the ascending aorta, with Ag / AgCl electrodes coupled to the veterinary electrocardiogram, brand DeltaLife, connected by USB port to the notebook and DeltaVet 7 software for recording and storing the tracings. In the modeling when using animals *in vivo* anesthetized with sodium thiopental (50 mg/kg), these were placed in dorsal decubitus on surgical boards and the four-clawed electrodes were attached to the legs and connected to ECG DL 660 (Delta Life). The rats from the PTU treated

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group, protocol *in vivo*, were anesthetized and the electrodes positioned for ECG examination. This Heart 9^0 mouse group treated with PTU, protocol *in Vitro* with the isolated and perfused heart with modified Krebs-Henseleit solution electrodes placed in the jar for picking up signals and ECG tracing (Figure 3).

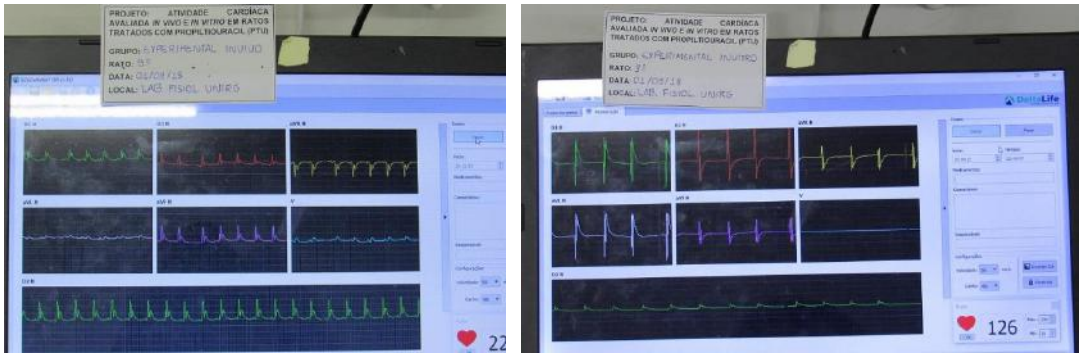

Fig.3: Capture of the electrocardiographic tracing of rats treated with PTU - Protocol in vivo and of heart isolated and perfused - Protocol in vitro. Laboratory of Physiology, UnirG, Gurupi-TO, Brazil, 2018.

2.3.Preparation of perfusion solution and Ag / AgCl electrodes

The perfusion solution that was used in the Langendorff preparation was modified Krebs-Henseleit since the commonly used in the Krebs-Henseleit solution is the carbonic acid/bicarbonate buffer, which requires a pressure of the carbogen mixture (95% O_2/5% CO_2).

In the absence of a carbogen cylinder, the buffer system was replaced consisting of phosphate/bicarbonate and used air aeration pressure the following chemical components (in mM): NaCl 125, KCl 4, $CaCl_2$ 2, $MgSO_4$ 1, NaH_2PO_4 1.2, $NaHCO_3$ 13.6 and Glucose 10 (Dynamic brand reagents), having an estimated osmolarity of about 305.6 mOsmol / L at the end.

Strictly speaking, osmolarity should have been measured and corrections made with the amount of glucose to 300 mOsmol / L, but in the absence of an osmometer, the 1000 ml solution thus prepared, was calculated at osmolarity. The pH of the solution was measured using a pH meter (checker, 0-14 pH range, 0.2 hi98103 precision, HANNA brand) and sometimes with a few drops of 0.1 M HCl, sometimes with a few drops of NaOH, 1 M, the mean final pH of the solution was set at 7.42 ± 0.03 (average of 7 preparations made).

The electrodes were prepared in the following manner: 1.5 g of agar was weighed into a Becker, where 30 ml of 3 M KCl solution was added. Hot mixed until boiled with a glass stick forming a paste which it was immediately sucked through a syringe and inserted into automatic pipette tips, pre-coupled to the chlorinated silver wire (AgCl) and left to solidify. The Ag wire (95% purity) was prepared by first immersing 3/4 of the metal into bleach (sodium hypochlorite) to form a dark portion with AgCl deposits. In the 1/4 Ag portion of the electrodes, the ECG claws were connected.

2.4. Variables analyzed

The variables obtained and analyzed in control rats and treated with PTU, *in vitro* or *in vivo*, were: heart rate (in BPM), amplitudes (in mV) of the P wave, QRS complex and T wave and intervals in the line isoelectric (in ms) of PR, QRS, and QT. All parameters were expressed as mean ± standard deviation, calculated from various measurements from the same ECG tracings corresponding to individual mice.

Heart rate (HR) was obtained by measuring the RR interval in milliseconds at ECG trace lead 2 at a scanning speed of 50 mm / s. This time, after being converted to seconds, the inverse of this value was calculated and the result was multiplied by 60 seconds, and the heart rate was expressed in beats per minute (BPM). The following is the example: RR interval = 136 ms, converted to 0.136 s. Then, FC = 1 / 0.136 = 7.353 x 60 s = 441.18 BPM.

The measurement of the amplitude of the P wave, identified by the analysis of the electric activity with positive polarity as a curve before the Q wave, was measured from an isoelectric line pointing the beginning and the apex, identifying the end of the P curve in the ECG tracing. The upper and lower limit of the P wave was determined by determining its electrical magnitude in mV. The determination of the P wave of each mouse was obtained by an average of five similar scores.

Measurement of the QRS complex voltage was extracted by analyzing the ECG trace from the lower bound of the complex to the upper limit of the R wave.

Voltage measurement or T-wave amplitude was performed from the upper limit of the waveform of the curve preceded by the S-wave to the lower limit of the isoelectric line of the heart that precedes the appearance of a new wave.

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The PR interval can be described as the measurement from the beginning of the P wave to the beginning of the Q wave of the QRS complex. The QRS interval was measured starting from the beginning of the Q wave until the end of the S wave, as shown in the image of one of the ECGs. The QT interval measurement was extracted from the beginning of the Q wave with negative polarity to the lower limit of the isoelectric line marking the end of the T wave and the beginning of a new Q wave.

2.5. Statistical analysis and data presentation

For the analysis and description of sample data in this study, we used the means as measures of central tendency, standard deviation as measures of dispersion of variability inherent in the samples, and coefficients of variation that were demonstrated in percentages.

For the inductive analysis, the *Student's* non-paired and two-tailed-test was used, with the significance level adopted at 5%, that is, all probabilities below 0.05 were considered significant using the Bioestat-5.3 program. The means and standard deviation are presented in the format of tables or graphs and software *Microsoft Office Excel* 2007.

III. RESULTS

The description of the results of the variables of the electrocardiographic profile of rats of the group treated with PTU had as reference the comparison with the parameters of ECG of healthy control group variables.

Thus there is the electrocardiographic profile of healthy rats (GC): ECG tracingProtocol *in vivo* examination 105 control group (Figure 4): R wave with 23% reduction and 75% decrease in wave amplitude S.

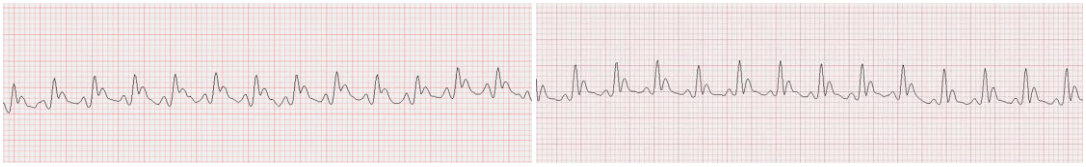

Fig.4 ECG tracing of the control group examination nº 105 and examination nº 121 - Protocol in vivo. UnirG, Gurupi-TO, Brazil. 2018.

In the ECG profile, the electrophysiological tracing was observed in 70% of the sample, with a decrease of 23% in the R wave amplitude and 75% in the S wave, and the other 30% in the control group with tracing presenting 20% of S wave reduction. In this way, one has to description ofECG results *in vivo* and *in vitro* for heart rate (in bpm); amplitudes of the waves P, QRS et (in mv); intervals of the isoelectric segments PR, QRS and QT (Table 1 and 2).

Table 1. Mean of parameters obtained from ECG tracings in vivo

PARAMETERS	CONTROL	PTU
FC (BPM)	412.24 ± 24.84; 10	235.36 ± 13.63; 10 *
P (Mv)	0.15 ± 0.02; 10	0.15 ± 0.03; 10
QRS (M +)	0.78 ± 0.14; 10	0.90 ± 0.36; 10
T (Mv)	0.18 ± 0.02; 10	0.44 ± 0.16; 10
PR (ms)	35.07 ± 1.70; 10	45.13 ± 1.96; 10 *
QRS (ms)	48.16 ± 3.1; 10	55.93 ± 3.35; 10 *
QT (ms)	90.26 ± 5.23; 10	186.70 ± 5.45; 10 *

Source: Authors (2018). Note: Cardiac parameters (mean ± standard deviation; sample size) obtained from traces *in vivo* of control and PTU treated rats. Heart rate (HR), P, QRS and T wave amplitudes and ranges of PR, QRS and QT isoelectric segments. * ($P \leq 0.05$).

Table 2 - Mean of parameters obtained fromECG tracings in vitro

PARAMETERS	CONTROL	PTU
FC (BPM)	134.76 ± 13.06; 5	99.35 ± 18.21; 5 *
P (Mv)	0.12 ± 0.003; 5	0.08 ± 0.01; 5 *
QRS (Mv)	0.70 ± 0.57; 5	0.58 ± 0.38; 5
T (Mv)	0.14 ± 0.01; 5	0.26 ± 0.08; 5
PR (ms)	27.68 ± 1.97; 5	49.65 ± 1.55; 5 *

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QRS (ms)	42.45 ± 1.7; 5	49.84 ± 5.01; 5 *
QT (ms)	115.12 ± 8.1; 5	203.41 ± 13.94; 5 *

Source: Authors (2018). Note: parameters obtained from in vitro ECG tracings in the Langendorff assembly (mean ± standard deviation; n sample) in the heart of control rats and treated with PTU. Heart rate (HR), P, QRS and T wave amplitudes and ranges of PR, QRS and QT isoelectric segments. * ($P \leq 0.05$)

In the experiments *in vivo* with anesthetized animals (Table 1), there was a 42.9% decrease in the mean HR value in the PTU group compared to the mean value found in the control. In the OCT group, the heart rate was significantly reduced to 235.36 ± 13.63 BPM (t = 14.97, P = 1.33 10-11)and when the control was 412.24 ± 24 BPM examination 162, there was a marked change in the RR interval in PTU treated rats while in the control group the HR was 412.24 ± 24, exam 143, where RR interval narrowing was observed (Figure 5).

Fig.5. RR interval measured at lead 2 with scanning speed 50 mm/s - PTU-treated mouse (Exam 162/18 - Protocol in vivo) and Rat Control Group (Test 143/18 protocol, vivo UNIRG Gurupi-TO, Brazil, 2018.

Inexperimental *vitro* model, the average value of the OCT group FC in Langendorff preparation (Table 2) were 99.35 ± 18 BPM, where a significant spacing in the RR interval, exam 199, was observed in rats treated with PTU, being 26% smaller in comparison to the control that presented HR equal to 134.76 ± 13 BPM, in which it is observed significantly (t = 3.53, P = 0.0077). smaller spacing RR interval, test 123 (Figure 6) This result agrees with those obtained *in Vivo*.

Fig.6. RR interval measured in the shunt 2 with scan rate 50mm/s in Mouse treated with PTU (Exam 199/18) - Protocol in vitro and Control mouse (Exam 123) - Protocol in vitro.

As for P wave, there was no functional alteration in its amplitude in the atrial chambers in this study *in vivo* performed in control animals and treated with PTU. As average wave amplitudes were 0.15 ± 0.02 P: mV in the control (GC) and 0.15 ± 0.03 mV in the OCT Group (GE), however, with the hearts isolated Langendorff system was observed in mice a 33% reduction OCT on P wave amplitude in comparison to healthy mice the average P wave amplitudes were: 0.12 ± 0.003 mV in the GC and 0.08 ± 0.01 mV in GE, with significant decrease (t = 4.88; P = 0.0012) in breadth P in isolated hearts of rats treated with PTU.

Already in the QRS complex amplitude ratio was found in experiments made *in vivo* conditions of two groups that, ventricular function assessed by analysis of QRS, presented statistically average amplitudes equal (difference was not significant), being 0.14 ± 0.78 mV in the control and 0.90 ± 0.36 mV in the OCT group. In

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studies done in vitro, this trend has also been observed, namely, showed no evidence of alteration of ventricular inotropic with 0.70 ± 0.57 mV in the control group compared to the lower average amplitude of 0.58 ± 0.38 mV obtained in the OCT group, although not significant (t = 0.39; P = 0.707). Similarly, there was no significant difference in the amplitude of the T wave, both protocols conducted in vivo as we conducted in vitro of rats OCTS, as compared to control group rats. As the PR interval was noticed an increase of 22% in protocols in vivo in rats OCT, i.e. the time needed for the electrical propagation through the atrial Chambers. This period in rats was 45 ± 2 OCT ms, i.e. higher compared to that achieved in healthy rats, in which the PR interval was 35 ± 2 ms in conducting atrial myogenic, being the PR interval of rats treated with PTU significantly longer (t = 12.3; P = 3.5. 10-10) showing a delay in the conduction disturbance between the SA and AV nodes.

The delay in conducting was corroborated with the in vitro studies of rats, in which the OCTS ECG tracings showed PR intervals with average value equal to 48.7 ± 1.55 DM, which corresponds to an increase of 43% compared to PR interval of 27.7 ± 1.97 ms found in co group role, with t = 19.6 significance; P = 4.8. 10-8.

In the range isoelétrico of the QRS complex was observed an increase of 13.89% in OCT group whose Protocol was in vivo, which had average value equal to 3.35 ± 55.93 ms and significant increase in rats treated with PTU (t = 5.4; P = 3.9. 10-5) compared to the control group, whose average interval was 48.16 ± 3.1 ms. The same behavior was observed in in vitro experiments with isolated hearts, where there has been 14.82% increase in the average range of QRS in rats treated with PTU, that was equal to 49 84 ± 5.01, ms. This increase is significative (t = 2.71; P = 0.026) compared to the average control group had this same interval a 1.7 ± 42.45 ms.

The measure of QT interval was extracted from the start of the Q wave with negative polarity to the lower bound of the isoelectric line that marks the end of the T wave and the beginning of a new wave Q. The difference obtained in this interval in rats compared to control OCTS are particularly notable, whether conducted in vivo protocols as in vitro. In experiments conducted in vivo found an increase of 106% in long QT syndrome in the OCT group compared to the control group. In rats, the average of the period OCT QT was 186 ± 5.45 ms, being this significant increase (t = 40.3; 4.3.10-19), because in the control rats the average value was 90 ± 5.23 Ms. In in vitro experiments in the Langendorff method, was found a significant increase of 77% in the QT interval with 203 ± 14 ms duration in rat ECG tracings OCT while in control rats the range QT was 115 ± 8 ms ((t = 9.7; P = 10-5).

IV. DISCUSSION

In this research it was ECG changes arising from the low level of hormones HT, i.e. in rats hipotireoideos by induction of the Oct. The explanation of the same was based on evidence obtained, too, in the studies of Klein and Ojamaa (2001) and Dillmann (2002), which showed the influence of HT for three distinct factors: biological Factor, neurofunctional and circulatory factor factor.

The biological factor is triggered when the reduction of the T3reprime gene expression protein synthesis of Alpha-myosin heavy chain (α-MHC) and increases the expression of the heavy chain of myosin beta (β-MHC)[33].(KLEIN; OJAMAA, 2001).

In neurofunctional T3altera reduction factor receptors of Catecholamines in the myocyte and reduces the modulation of cardiac autonomic nervous system function, both in Nice stimulation as rogue [34].(DILLMANN, 2002).

As for the circulatory facto, there is evidence that reduced T3 changes angiogenesis with decreased capillary density, in addition to increased peripheral vascular resistance [33].(KLEIN; OJAMAA, 2001).

It has been found in the protocol in vivo, 42.9% fall in heart rate in the group treated with PTU compared to control, is the same behavior observed in the protocol in vitro com fall of 26% of heart rate. The evidence that links biological factor influence on cardiac cronotropismo, through the action of T3na gene expression of several proteins related to contractility ischemia. These corroborate findings with studies of Ladenson et al. (1992)[35] to demonstrate the increased eleven times, steady-state of MHC gene expression, with minimum reduction of β-MHC, and these findings are evidence of the relationship of the modulation role of T3 in cardiac contractility, with relevance in alleviating speed in the presence of hormonal deficit contraction.

Ohga et al. (2002)[36]. assert that the myocardial dysfunction in hypothyroidism is associated with increased expression of the heavy chain of β-MHC, reduction in Ca2 + ATPase of the sarcoplasmic reticulum, and ryanodine receptors and the increase of Fosfolambam.

In the survey of Danzi, Ojamaa e Klein (2003)[37]. gene transcription of myosin heavy chain of alpha-(α-MHC) protein with contractile function, related to rapid contraction and calcium ATPase (SERCA2) enzyme found in the membrane of the sarcoplasmic reticulum is responsible for absorbing the Ca + 2 during

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Repolarization, and mediated by thyroid hormones, are evidence for the bradycardia in hypothyroidism.

In the studies of Tang et al. (2005) [11]. the bradycardia was found as a cardiac functional alteration in hypothyroidism, where reducing triiodothyronine cause impairment of contractility of cardiomiocitos by a change in Ca 2 + ATPase in the endoplasmic sarcoplasmic reticulum (SERCA2) and Alpha-myosin heavy chain (α-MHC).

The bradycardia observed in this research has also been found in studies that link the factor neurofunctional, where T3 appears to act on the sensitivity of the nerve system as nice. The identification of low-frequency components decrease heart rate (LF) and high frequency (HF) observed during the study of heart rate variability (VCF) indicate the state of inhibition of the autonomic nervous system modulation, in especially nice stimulation, and reduction of heart cronotropismo in the presence of hypothyroidism. [38]. (GALETTA et. al., 2008).

Spear e Moore (1973)[39]. ensure that the sinoatrial node was more sensitive to vagal stimulation and that changes in heart cronotropismo can increase the atrioventricular node's response to influences of the autonomic nervous system. These factors reveal the effects of as on pacemaker activity, spread and breadth of the cardiac cycle, as for example, in experimental studies with animals was observed the evolution of arrhythmias arising from the elevation of the activity autonomous. Mcdevitt et al. (1968)[40]. describe that even with inhibition of the autonomic nervous system in patients with hypothyroidism, heart rate was lower than expected for the age. However, in the same experiment, the pace was higher than expected by age in patients with hyperthyroidism. Such findings indicate that the heart rate is mediated by the influence of thyroxine on cardiomiocitos and not by increased sympathetic stimulation of the Catecholamines for excess thyroid hormones [41].(HARRISON,1964).

In the experiments of Thier, Gravenstein and Hoffmann and colleagues, developed in 1962, an experimental model *in vitro* os Atria hipertiroidismo animals showed a fast heart rate, compared to animals eutireoideos, the result of the relationship of thyroxine in the heart cronotropismo [42,43,44].(MENDELSOHN; ANTONIS, 1961; THIER; GRAVENSTEIN; HOFFMANN et al., 1962; CRAVEY; GRAVENSTEIN, 1965).

Any location of the heart is, a priori, excitable self, however, the cardiac pacemaker or sinoatrial node (AS) is the higher frequency of cardiac action potentials fire spontaneous (PAC), with this, it's generator and controller of the cardiac rhythmicity and seem to occur due to an influx of positive charges through specialized ion channels located in the pacemaker cells, which are activated and inactivated following a spontaneous pattern sequence for the successive shots PAC´s [45].(SILVERMAN; HOLLMAN, 2007).

The influx by ion channels are described as "channels activated by hyperpolarization" (HCN), because, at the end of the membrane potential, Repolarization of a previous PAC these channels, that were until then closed, will open gradually allowing the influx of cations (K^+e Na^+) generating the spontaneous depolarization is needed to achieve the next clock CAP threshold for activation of channels Ca^{+2} voltage-type-dependent L and the current influx of calcium [46].(ACCILI et al., 2002).

The channels HCN, today is well known and characterized molecularly, are part of the family of cyclic nucleotides channels activated by hyperpolarization, belonging to the superfamily of potassium channels with higher density in the SA node cells and closing on last part of the diastolic depolarization [47].(BARUSCOTTI et al., 2005).

Despite being described in cardiac tissue, the channels HCN are found also in the brain, where they operate in the spontaneous generation of action potentials. The magnocellular fibers core supraoptic neurosecretory neurons in the hypothalamus have channels HCN modulated by the nitrérgico system through the gaseous Messenger nitric oxide (NO), which control the clock rate of these neurons by inhibiting the excitability and thus promoting a reduction in the release of vasopressin and oxytocin [48]. (SILVA et al., 2016).

The mechanisms are still unknown, however, there are hypotheses and some evidence that the NO acts directly on the canals HCN inducing a significant reduction in the current influx of cations to bind the cysteine residues forming complexes of S-nitrosotióis [48]. (SILVA et al., 2016). Such evidence open perspectives about the mechanism of action in controlling spontaneous electrical excitability in the SA node when you correlate the nitrérgico system with the channels HCN to explain the bradycardia and the delay in several segments of the ECG observed in animals treated with PTU, *in vivo,* and *in vitro,* with the possibility of hypothyroidism to be associated with greater production of NO.

Bradycardia effect, as well as the consequent delays in cardiac excitability and transmission observed in hipotireoideos rats, can also be interpreted under another approach: the important role of adenosine on neuronal

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excitability and synaptic transmission by endogenous modulation. This occurs by means of receptors A1 e A2 in the cardiovascular control exercised by the nucleus of the solitary tract (NTS), through their autonomic projections (sympathetic and parasympathetic). NO is synthesized by The Synthase (NOS) in neurons of NTS, participating in the hypotensive effect and bradycardia triggered by activation of A2A adenosine receptors and activation of astrocytes releasing Ca + 2intracelular, which can produce the [49].(PRIVIERO, 2002).

In this study found no change in the amplitude of the P wave in rats treated with PTU in an experiment *in vivo*. However, the experiment *in vitro* reduction of 33% in the amplitude of the P wave. These findings confirm the results of Panciera (1994), where the experimental model of hypothyroidism in dogs the results reveal reduction of the amplitude of the P and R-wave in ECG tracings. These changes were reversible after hormone replacement. In the work of OZTURK et al. (2012)[50]. the findings showed a deficit in the right atrium with reduced volume and passive emptying fraction and increased in volume and active fraction in the presence of hypothyroidism.

The results of this survey showed no significant differences in the amplitude of the QRS complex, both in vitro and in vivo. Madias (2008) [51] declares that the pericardial effusion and the accumulation of fluid in the place of generation of the action potential, besides reducing the electrical resistance of the extracellular space, are the reasons of the heart and heart of extra influence low voltage of the complex QRS, respectively. Both situations occur simultaneously in hypothyroidism.

In studies of Karatay (1993, apud in Bruchet al., 2001) [52]. the ratio of the low-voltage QRS and pericardial effusion was associated with the driving deficit by the accumulation of fluid in the pericardial space and change in eletrogênese are voltage attenuation factors of the QRS.

Although this work has not found evidence of changes in the amplitude of the T wave in the presence of hypothyroidism, several studies point to changes in myocardial Repolarization in particular in the left ventricle. The findings of Alonso et al. (2015) [53] indicate that hypothyroidism Repolarization changes are secondary to a reduction in external transient potassium current (Ito), while increasing the calcium current of type L (ICa-L). As well as the observed in ECG, impair the T wave and action potentials in patients hipotireoideos as in experimental animal models.

In search of Al-Zaidi, Abdul-Ghafour, and Al-Farttoosi (2010) [54]. in patients with hypothyroidism ECG tracings showed flat and inverted T waves in 27.8% of the sample result expressive compared to eutireoideos patients who have the same behavior on a path in just 3.4%.

Baker research, Satpathy and Samal (2017) [55]. in a sample of 60 patients with hypothyroidism, in ECG found 40% of low voltage of the complex, 26% of pericardial effusion with diastolic deficit followed by 23.3% flattening of the T wave.

The survey found an increase of 22% in the period of electrical propagation in atrial Chambers in group in vivo de OCT, treated rats with prolongation of the PR interval, this delay in electrical conduction was corroborated in estudyes in vitro observed an increase of 43% in PR interval in ECG tracings on experimental sample compared to the control group. Changes in levels of hormones tiroidianos seems to interfere with the electrical conduction of the atrioventricular node, evident in the increase in PR prolongation of animals of this study.

The findings of Cheng et al. (2009) [56] indicate that the prolongation of PR is associated with the functional activity of the heart change increase in atrial fibrillation (AF), need to use pacemaker and mortality, suggesting that it is not benign in the findings of Routine ECG, as earlier studies indicated. In another study by Cheng et al. (2015) [57]. the finding of the lengthening of the PR interval showed this condition as a Predictor for the emergence of FMD free from any influence of age, sex, and hypertension.

The studies of Sadr-Ameli et al. (1987) [58] point to evidence of the influence of the autonomic nervous system in the PR interval, this condition is explained by the fact that vagal stimulation and inhibition nice promote sinus cycle length elevation and increase atrioventricular nodal conduction, however, vagal blockade reduces the size of the sinus cycle and optimizes the atrioventricular nodal conduction anterograde, these findings corroborate with data already studied previously in animals and humans.

In Schenck, Rizvi, and Lin (2006) [59]. the findings of the cardiac activity in hypothyroidism, in addition to reducing heart rate, the prolongation of the PR interval, the low amplitude of the P wave and the QRS complex, are evidenced driving delays on the electrocardiographic tracings atrioventricular.

En el experimento hubo aumento de isoelétrico QRS 13.89% observado en el grupo PTU en protocolosin vivo, en comparación con la muestra de control. Estos resultados fueron acompañados en corazones aislados vitrocom experimentosin, 14.82% de aumento en la gama media del QRS en ratas tratadas con PTU, en comparación con el control, con $P \leq 0.05$ de significación.

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The results of this survey corroborate with the works of Sarma et. Al. (1990) [60] and Fredlund and Olsson (1983) [61], the lengthening of the QRS complex and QT are related to changes in cardiac activity in the presence of hypothyroidism. Silvet et al. (2001) [62] and Goat-Schnurbus et al. (2003) [63] found that patients with left ventricular systolic change the QRS elongation were associated with a high incidence of mortality.

In the works of Tiryakioglu et al. (2010) [64] the left ventricular systolic dysfunction in hypothyroidism is associated with the presence of interstitial edema, fibrosis, myocardial hypertrophy by increasing peripheral vascular resistance and the change in contracts protein synthesis by the deficit of T3 (Triiodothyronine).

In studies of Pearce et al. (2010) [65] changes of vascular resistance, peripheral and pulse vasoconstricção were observed and signals associated with prolongation of the QT interval and QRS complex these changes with the incidence of tachyarrhythmia.

In the studies of Gintant, Gallacher and Pugsley (2011) [66] sodium channel currents (In) guarantee the rise and high speed of propagation of the action potential along the ventricular myocardium. Changes in the electrical conduction of the ventricles are associated with reduction In cardiac and current the excitability of this change is manifested with the prolongation of the QRS COMPLEX in ECG tracings.

Kweon, Park, and Cho (2007) [67] described that, among the cardiovascular changes in absence of tiroidianos hormones during the hypothyroidism, heart failure is highlighted with prolongation of the QRS COMPLEX associated with the high rate of mortality. Occasionally there is ventricular tachycardia, however, in this study showed that the replacement of L-Thyroxine reduces ventricular arrhythmia and sudden death.

This research identified that the QT interval increased by 106% in the protocol in alive and in 77% in vitro em compared to experiment in control sample ($P \leq 0.05$). These results resemble studies of Bosch et al. (1999) [68]. where the presence of increased QT in the experimental animal model showed a delayed rectifier K chain (LKs) and was admitted as responsible for the delay of Repolarization in ventricular cardiac myocytes membrane.

In studies of Ferrer et al. (2012) [28] found a prolongation in QTc interval in the presence of hypothyroidism evidencing a change on ventricular Repolarization and showed a 90% increase in the duration of the action potential in cells myocardial hipotireoidianas. According to the authors, this change may be associated with the reduction in the Repolarization of K + currents.

In search of Rubinstein and Binah (1989) [69]. QT elongation was associated with the elevation of the ventricular action potential in hipotireoideos animals, this change was attributed to the reduction of the magnitude of the current L-type Ca (LCA) on the membrane cardiomyocyte.

Yao and Eghbali (1992) [70], in an animal study, they found evidence of the action of thyroid hormones in preventing fibrosis by inducing selective suspension of production of collagen type I this change associated with the excess extracellular proteins causes of edema and seems to contribute to increasing of QT dispersion.

In this study it is concluded that the OCTS administration induced by hypothyroidism in animals, evidenced by increased volumes of the thyroid gland in the animals treated, being this clinical condition promoter of cardiac electrical activity changes obtained in the parameters obtained from ECG tracings.

Cambios funcionales en el corazón se encontraron en la parte más grande en el cronotropismo que en inotropismo, evidencia por bradicardia y principalmente en extensiones de algunos de los principales intervalos en OCT trataron ratas, tanto utilizando el in vitro preparación Langendorff en vivo en los animales anestesiada.

The results obtained by your pioneering character of the methodological point of view, related to Langendorff preparation, can be a motivating factor for the development of future regional local projects addressing the neuroendocrine Physiology axis hypothalamic-pituitary-thyroid, associated directly or indirectly the cardiovascular events. This perspective can subsidize actions in health, especially in the northern region of Brazil.

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