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Original Article

Association between maternal hypothyroidism, baby birth weight, and adult cardiovascular disease risk: insights from ECG measurements

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Abstract: Objectives: Thyroid hormone (TH) deficiency during pregnancy may affect cardiovascular function in offspring rats. This study aimed to evaluate the effect of TH deficiency during gestation, on the electrocardiogram indices of young and middle-aged offspring of male rats. Methods: Eight female rats were equally divided into hypothyroid and control groups. The hypothyroid mothers received 0.025% 6-propyl-2-thiouracil (PTU) in drinking water throughout pregnancy, while control mothers consumed only tap water. Following birth, male rats from each group were observed for 4 months (young age) and 12 months (middle-aged). The group known as fetal hypothyroid (FH) consisted of rats born from hypothyroid mothers. The serum T4 and TSH concentrations from mothers and newborn male rats were assayed at the end of gestation. Lead II electrocardiogram (ECG) was recorded for 5 minutes using Power Lab, AD Instruments. Results: There was a significant rise in the P wave voltage in young FH rats, whereas, it was decreased in middle-aged control and FH rats. The voltage of QRS decreased and its duration increased in the young and middle-aged FH rats compared to the corresponding control groups. Duration and voltage of the T wave were significantly altered in the young and middle-aged FH groups. PR and QT intervals significantly increased in the young and middle-aged FH groups compared to their controls. Conclusions: Maternal hypothyroidism affected the electrocardiogram indices of offspring rats, possibly signaling cardiovascular problems later in life.

Keywords: Aging, electrocardiogram, fetal hypothyroidism, rat

Introduction

Thyroid hormones (TH)s play a crucial role in growth, development, and cell metabolism [1]. They act as the main regulators of tissue metabolism, ensuring the normal function of nearly all tissues [1]. The cardiovascular system is one of the most important targets for THs [2]. THs have inotropic, chronotropic, and dromotropic effects on the heart [2]. Chronotropic changes in hypothyroidism are indicated as bradycardia, narrow pulse pressure, low P and QRS voltages, prolonged PR and QT intervals, fluttered or reversed T wave, and heart block [3-5]. Additionally, changes in heart rate variability and turbulence have been observed in these patients [4]. Thirty percent of hypothyroid patients have pericardial effusion leading to an increased intra-pericardial pressure, which may affect the electrocardiogram [6].

The development of numerous adult diseases can be attributed to disruptions in fetal growth and unfavorable conditions within the womb. Congenital hypothyroidism is defined as a lack of THs at birth [7]. The incidence of this disease is 1 in 2000 to 3000 live births, making it one of the most common congenital endocrine diseases [8]. Some studies have shown that rat maternal TH deficiency increases the risk of cardiovascular disease in their adult offspring

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hypothyroid rats [9]. A human study revealed that heart rate variability is reduced in 36 and 48 month-old congenital hypothyroid patients [10]. Furthermore, it has been observed that cardiac tolerance to ischemic reperfusion is reduced in fetal hypothyroid adult rats [11].

Although aging and hypothyroidism can impact the electrocardiogram [12], there is limited research on how congenital hypothyroidism affects the electrocardiogram of children as they grow older. Considering that pregnant mothers are screened for thyroid diseases during pregnancy, conducting a clinical trial on hypothyroid mothers who are not treated is ethically contraindicated. Therefore, this study was conducted on animals to demonstrate the overall impact of maternal hypothyroidism on the ECG of their offspring.

Materials and methods

Animals and care

Eight healthy female Wistar rats, weighing between 190 and 225 grams, were randomly divided into two groups: control mothers and hypothyroid mothers. The researchers and laboratory staff responsible for assigning animals to different experimental groups were aware of the group allocation during the initial stages of the study. Once the study was completed, the authors analyzed the data. Control mothers consumed only tap water, while the hypothyroid mothers received 0.025% 6-propyl-2-thiouracil (PTU) (obtained from Sigma, Germany) in drinking water throughout pregnancy. After delivery, 16 healthy male offspring rats from the control mother and hypothyroid mother groups were randomly selected. In each group, eight rats were sacrificed after birth for blood sampling, and the remaining eight were followed for 4 months (young age) and 12 months (middle-aged). The offspring of male rats born from hypothyroid mothers were considered the fetal hypothyroid (FH) group. The sample size was calculated using the equation provided in the report by Arifin et al. [13]. Animals that appeared sick during the experiment were excluded from the study, and some animals died during blood sampling, resulting in a decrease in the number of rats in some groups. **Figure 1** illustrates the animal groups and their corresponding sample sizes.

Rats were housed in standard conditions (22±2°C, 12/12 h light-dark cycle) with free access to a standard rat chow diet (Pars Co. IR) and tap water *ad libitum*. All animals were pair-housed in environmentally enriched laboratory cages (42×26.5×15 cm) with aspen woodchip bedding, which was changed twice a week. The cages were washed with soap and water once a week, and the animals' water was replaced every 3 days.

Ethics approval

All procedures were performed under the standards for animal care established and approved by Iranshahr University of Medical Sciences; in Iranshahr, Iran (Ethics code: IR.IRSHUMS.REC.1398.004).

Determination of body weight

The body weights of male offspring rats and their corresponding control rats were measured at birth, at the end of the fourth month, and at the end of the twelfth month.

Blood collection and measurement of TSH and T4 levels

Blood samples from the mothers and eight neonate rats were collected after delivery in microcentrifuge tubes containing EDTA (5 mg/ml), centrifuged (3000 g, 10 min at 4°C), and the plasma was stored at -20°C for measurement of THs. Plasma concentrations of T4 were measured using the ELISA method (Pishtazteb Zaman Co., Iran), and plasma concentrations of TSH were measured using a Rat TSH ELISA kit (Demeditec, Diametric Diagnostics, GmbH, Germany). Intra-assay coefficient of variations for assays were 4.8% for T4 and 2.9% for TSH.

Electrocardiogram measurement

After the procedures, male offspring rats aged 4 and 12 months old from each group were anesthetized with an intraperitoneal (*i.p.*) injection of ketamine (80 mg/kg) and xylazine (8 mg/kg). Due to inadequate laboratory facilities, the ability to measure ECG in newborns was limited. Anesthesia was necessary to record the ECG in rats, with a high risk of mortality during the procedure. No pain-relieving medications were prescribed in this study due to dis-

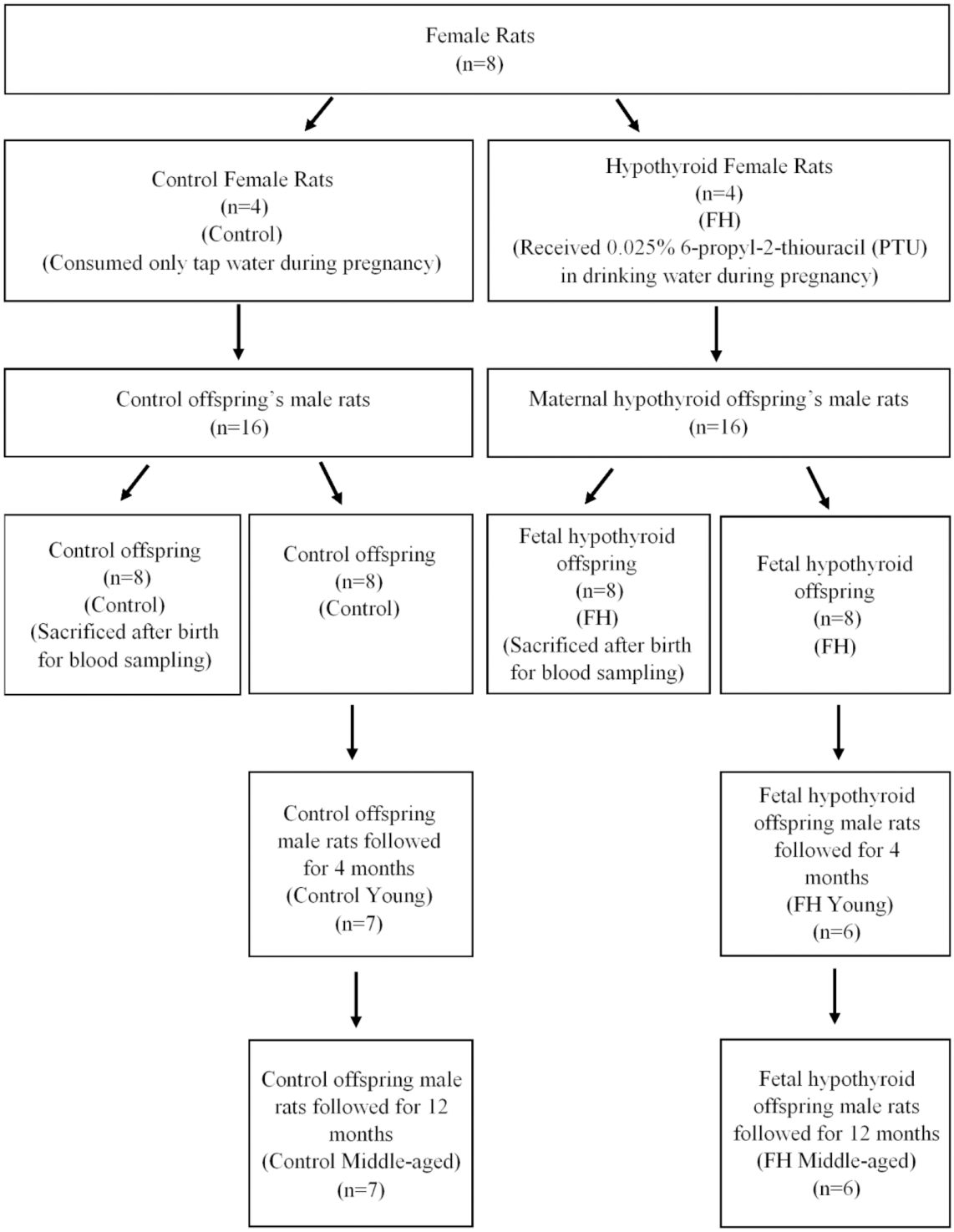

Figure 1. The animal groups and their respective sample sizes.

ruptions in ECG recording. A Lead II electrocardiogram was recorded for 5 minutes using the Power-Lab apparatus from ADInstruments in Australia to calculate various voltages, intervals, and durations. Following standard protocol, the electrodes were placed on the skin at the xiphoid cartilage, with the negative electrode on the right shoulder and the positive

Table 1. Body weight in offspring rats (Mean ± S.E.M.)

	New Born		Young		Middle-aged	
	Control	FH	Control	FH	Control	FH
Body Weight (g)	6.2±0.09	4.99±0.11*	247±8	277±9+	416±15	397±12

Body weight in young (4 months) and middle-aged (12 months) control and FH groups. FH group is the male rats born from hypothyroid mothers and the control group are the male rats born from normal mothers. The data are presented as mean ± S.E.M. with n = 7; for young and middle-aged control groups and n = 6; for young and middle-aged FH groups. Data were analyzed using a t-test. *$P < 0.05$ compared to the control newborn; +$P < 0.05$ compared to the young control.

Table 2. Levels of THs at the time of delivery in mothers and in offspring rats (Mean ± S.E.M.)

	Mother		Offspring		Offspring		Offspring	
	At the time of delivery		At the time of birth		4 months (young)		12 months (middle-aged)	
	Control mother	Hypo mother	New born of control	New born of congenital hypothyroidism	Control	FH	Control	FH
TSH (ng/ml)	1.8±0.3	19.2±1.4**	3.4±0.6	12.3±1.4++	6.1±0.3	6.6±0.5	5.3±0.3	5.5±0.5
T4 (μg/dl)	3.0±0.4	0.7±0.1**	0.9±0.1	0.4±0.04++	3.5±0.2	3.8±0.1	2.5±0.08	2.98±0.2

**$P < 0.001$ compared to the control mother; ++$P < 0.001$ compared to the newborn of the control. There was no significant difference between the 4-month-old offspring groups and their controls, as well as the 12-month-old offspring groups and their controls. The data analysis was conducted using a t-test.

electrode on the left leg [14]. The electrodes were connected to a Bioamp amplifier (ADInstruments, Australia) and digitized through an A/D converter Power-Lab 8sp (ADInstruments, Australia). The LabChart software version 7 for Windows 10 was used to analyze the digital recordings. Activities were recorded at a rate of 4000 per second and refined to a frequency of 50 Hz. The ECG signal was calibrated to a paper speed of 25 mm/s with a sensitivity of 10 mm = 10 mV [14]. All testing procedures were conducted in a double-blind manner by a laboratory expert. After the experiment, rats were euthanized using a humane method in accordance with ethical guidelines for animal research. The rats were placed in a standard chamber and exposed to CO_2 gas to induce anesthesia and ultimately death.

Statistical analysis

Statistical analysis was conducted using SPSS software version 15, and the data were presented as the mean ± SEM. Comparisons were made using a t-test and one-way analyses of variance (ANOVA), followed by a Least Significant Difference (LSD) test. A *p*-value of less than 0.05 was deemed significant. Any outliers detected by the software were excluded. GraphPad Prism software version 8 was used to generate high-quality graphs.

Results

Body weight

Newborn FH rats had significantly lower body weights compared to control rats as shown in **Table 1**. After 4 months, the body weight of young FH rats was significantly higher than that of the young control group. However, no significant difference in body weight was observed between the middle-aged FH and control groups.

Serum TSH and T4 levels

At the time of delivery, the mean plasma TSH was significantly higher in hypothyroid mothers (19.2±1.4 ng/ml) compared to control mothers (1.8±0.3 ng/ml, $P < 0.001$). Simultaneously, the mean plasma T4 concentration was significantly lower in hypothyroid mothers (0.7±0.1 μg/dl) compared to control mothers (3.0±0.4 μg/dl, $P < 0.001$), indicating successful induction of hypothyroidism by PTU (**Table 2**). This condition was transferred to their offspring, resulting in newborn fetal hypothyroid rats having lower T4 levels (0.4±0.04 ng/ml) and higher TSH levels (12.3±1.4 μg/dl) at the time of delivery compared to the corresponding control group (T4: 0.9±0.1 ng/ml, P < 0.001; TSH: 3.4±0.6 μg/dl, $P < 0.001$).

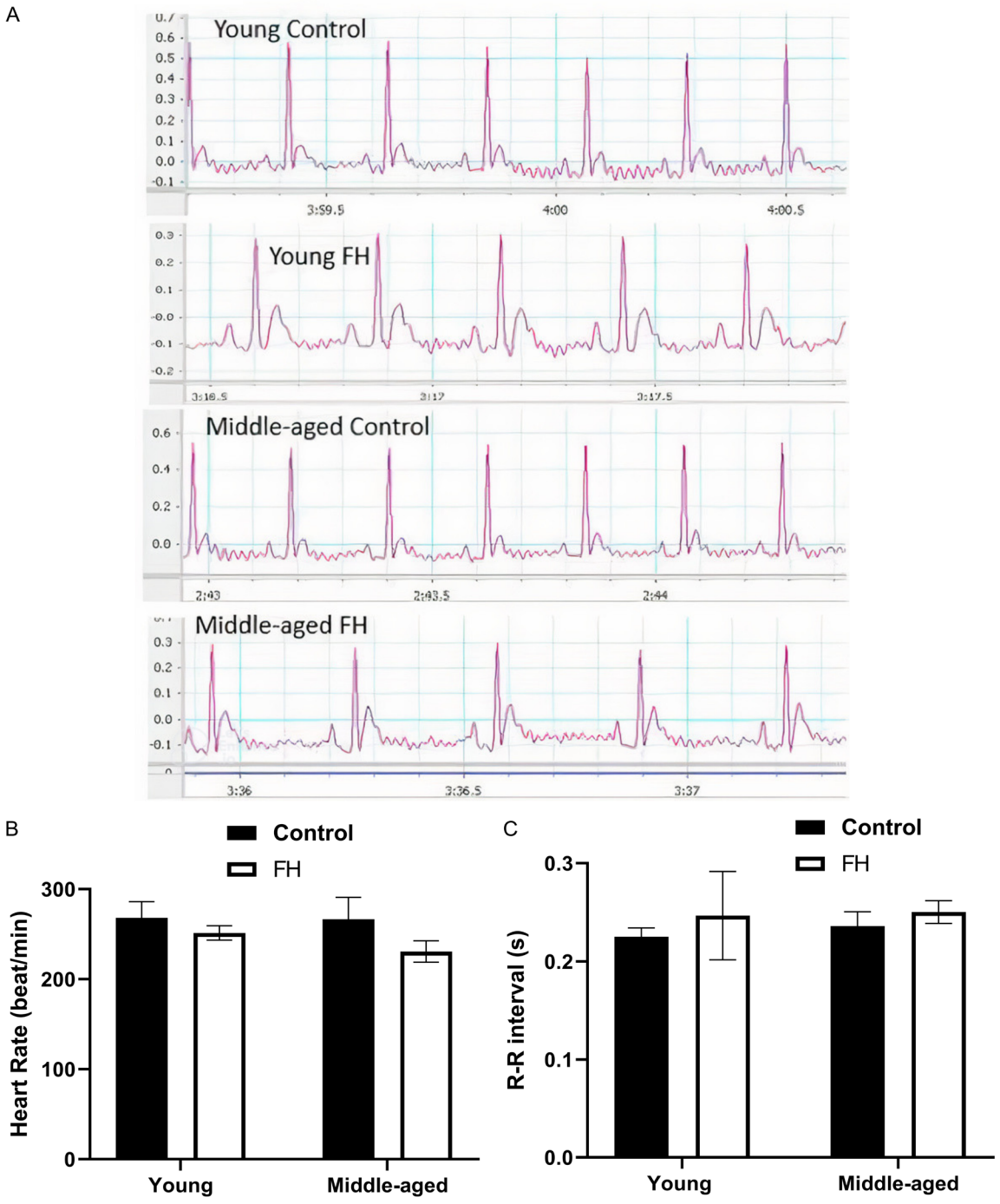

Figure 2. Heart rate and R-R interval were extracted from lead II electrocardiograms. A: The electrocardiogram images of four groups. B: Heart rate. C: R-R interval in young (4 months) and middle-aged (12 months) control and FH groups. The FH group consisted of male rats born from hypothyroid mothers, while the control group consisted of male rats born from normal mothers. The data are expressed as mean ± SEM with n = 7; for young and middle-aged control groups and n = 6; for young and middle-aged FH groups. Data analysis was conducted using one-way ANOVA followed by LSD test.

Electrocardiographic measurements

Figure 2A displays the ECG image of four groups.

Heart rate and RR interval: No significant differences were observed in heart rate (HR) and R-R interval between FH and control groups in young and middle-aged rats (**Figure 2B** and **2C**).

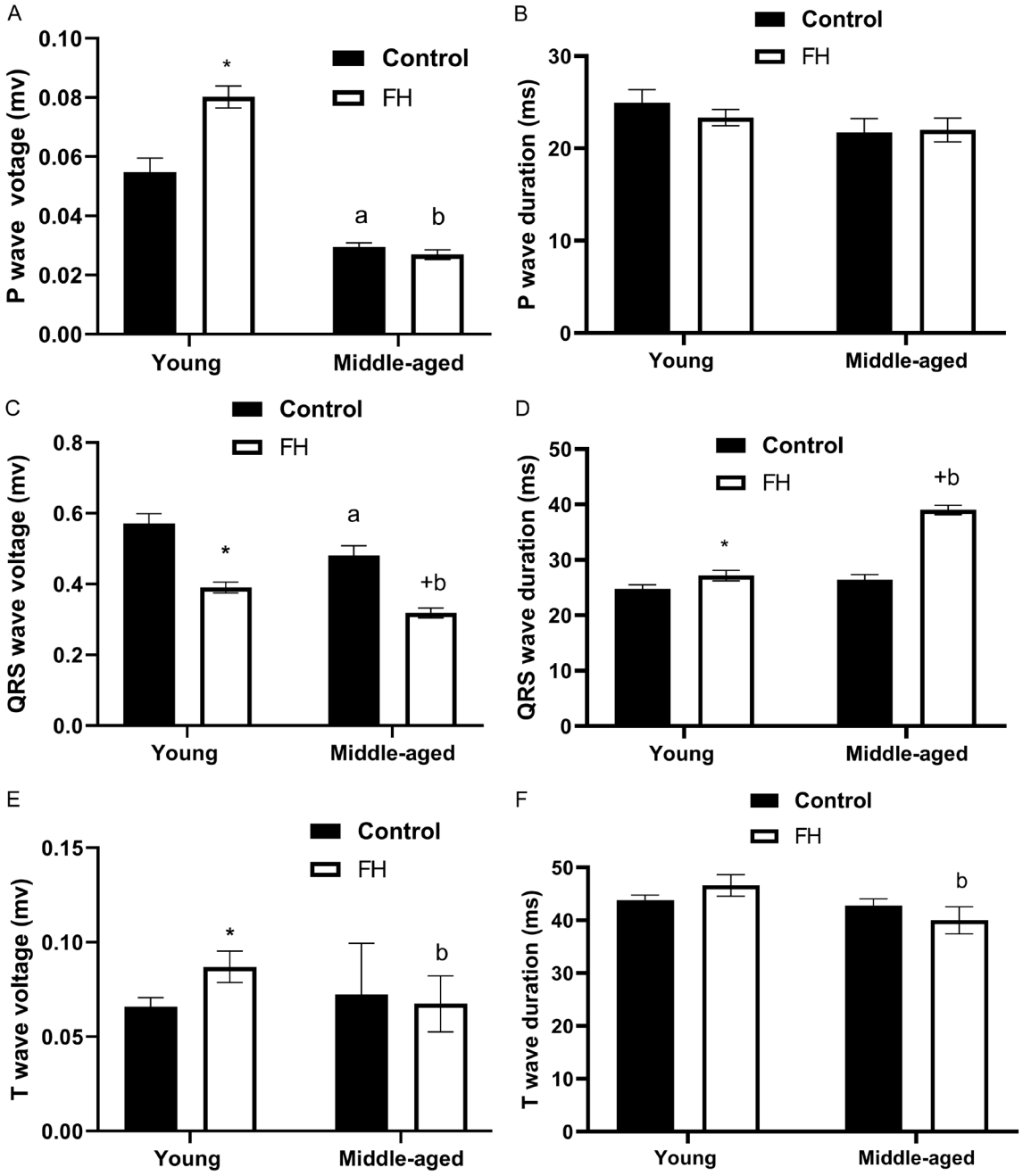

Figure 3. Voltage and duration of P, QRS, and T waves were extracted from lead II electrocardiograms. A, C, E: The voltage. B, D, F: The duration of waves in young (4 months) and middle-aged (12 months) control and FH groups. The data are presented as mean ± SEM with n = 7; for young and middle-aged control groups and n = 6; for young and middle-aged FH groups. Data analysis was performed using one-way ANOVA followed by LSD test. $^{*}P < 0.05$ compared to the young control; $^{+}P < 0.05$ compared to the middle-aged control; $^{a}P < 0.05$ compared to the young control; $^{b}P < 0.05$ compared to the young FH.

P wave: The voltage of the P wave in the young FH group was significantly higher than the control group (0.08±0.003 vs. 0.055±0.004 mV, $P < 0.001$) (**Figure 3A**). As rats aged, the voltage of the P wave significantly decreased in both control (0.029±0.001 vs. 0.055±0.004 mV, $P < 0.001$) and FH groups (0.027±0.002 vs. 0.08±0.004 mV, $P < 0.001$). There were no significant differences between the control and FH groups in the duration of the P wave for young and middle-aged rats (**Figure 3B**).

QRS wave: The voltage of the QRS wave in the FH group was significantly lower than controls

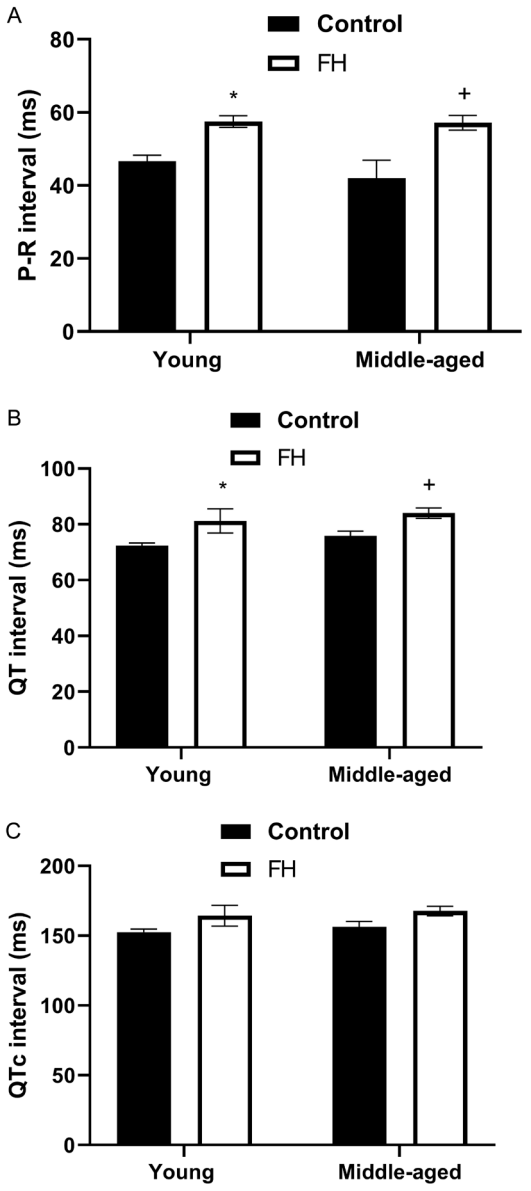

Figure 4. The PR, QT and QTc interval are extracted from lead II electrocardiograms. A-C: The interval of waves were extracted from lead II electrocardiograms in young (4 months) and middle-aged (12 months) control and FH groups. The data is presented as mean ± SEM with n = 7; for young and middle-aged control groups and n = 6; for young and middle-aged FH groups. Data analysis was performed using one-way ANOVA followed by LSD test. $^{*}P < 0.05$ compared to the young control; $^{+}P < 0.05$ compared to the middle-aged control.

in young (0.32±0.01 vs. 0.48±0.028 mV, $P < 0.001$) and middle-aged rats (0.39±0.01 vs. 0.57±0.027 mV, $P < 0.01$) (**Figure 3C**). As rats aged, the voltage of the QRS wave significantly decreased in both control (0.48±0.028 vs. 0.57±0.027 mV, P < 0.01) and FH (0.32±0.01 vs. 0.39±0.01 mV, $P < 0.001$) groups.

During aging, the duration of QRS significantly increased in both the control and FH groups, with a greater increase observed in the FH group. In the control group, the duration was as follows: young: 31±0.45 ms vs. middle-aged: 24.8±0.7 ms, $P < 0.05$. In the FH group, the duration was as follows: young: 39.5±1.6 ms vs. middle-aged: 27.4±0.9 ms, $P < 0.01$ (**Figure 3D**).

T wave: The voltage of the T wave was significantly higher in the young FH group compared to their corresponding control groups (0.087± 0.004 vs. 0.066±0.002 mV, $P < 0.05$) (**Figure 3E**).

During the aging process, the voltage of T waves decreased in the middle-aged FH group compared to the young FH group (0.067±0.006 vs. 0.087±0.004 mV, $P < 0.05$) (**Figure 3E**).

Significant changes in the T wave duration were only observed in the FH group. T wave duration in the middle-aged FH group was significantly lower than in the young FH group (40.78±1.3 vs. 46.6±2 ms, $P < 0.05$) (**Figure 3F**). Aging caused no difference in the duration of the T wave in the control group.

PR interval: The PR interval was significantly higher in the FH group than in the control group in both young (57.5±1.4 vs. 46.6±1.7 ms, $P < 0.01$) and middle-aged rats (57.3±1.7 vs. 42±4.9 ms, $P < 0.001$) as shown in **Figure 4A**.

QT interval and QTc interval: The QT interval was higher in the FH group compared to controls in both young (81.2±4.3 vs. 72.3±0.92 ms, $P < 0.05$) and middle-aged rats (84.2±2.6 vs. 75.9±1.7 ms, $P < 0.05$) (**Figure 4B**). However, no significant differences were found between the two groups in the QTc interval (**Figure 4C**).

Discussion

We evaluated the differences in electrocardiographic patterns in young and middle-aged male rats born to mothers with hypothyroidism. The results showed significant unfavorable alterations in the voltage and duration of P, QRS, and T waves, as well as PR and QTc intervals in the young and middle-aged fetal hypothyroid rats compared to the control group.

Cardiac arrhythmias are more common in the atria than the ventricles during the aging process [15]. Studies have indicated that aging results in a decrease in pacemaker cells within the sinoatrial (SA) node, along with atrial enlargement and an increase in fibrous and fatty tissue in older individuals [16, 17]. Additionally, aging affects cellular and molecular pathways within the heart [18]. Therefore, the reduced P-wave voltage observed in both the control and FH groups may be attributed to the effects of aging.

The present study found that the voltage of QRS was lower and its duration was higher in young and middle-aged FH rats compared to the control group. Additionally, the voltage and duration of the T wave were higher in young FH rats and lower in middle-aged FH rats. The QRS wave represents ventricular depolarization and contraction, while the T wave reflects ventricular repolarization. Oner et al. reported ventricular dysfunction in patients with congenital hypothyroidism [19]. Numerous studies have documented reduced P and QRS voltages and inverted or flat T waves in hypothyroid patients [3-5]. The current study observed similar trends, with the FH group showing a more pronounced decrease in QRS amplitude as they aged. This aligns with research by Michelis et al., who demonstrated that aging alters renal structure and function, potentially leading to potassium imbalance and hyperkalemia [20]. Elevated serum potassium levels are known to reduce P and QRS wave amplitudes and increase T wave peak amplitude [21]. While we did not measure serum potassium levels in this study, the observed changes in QRS and T wave voltages in the middle-aged control group could be attributed to these factors. Although aging can affect the amplitude of all ECG waves, our findings suggest that these effects are more pronounced in FH rats.

This study found that PR intervals (representing conduction time from the sinus node to the ventricles) and QT intervals (reflecting ventricular repolarization inhomogeneity) were significantly longer in both young (19% and 12%, respectively) and middle-aged FH rats (27% and 10%, respectively) compared to their corresponding control groups. These findings align with previous research: Wald et al. observed prolonged PR and QT intervals in hypothyroidism [6], and another study reported longer QTc intervals and lower QRS voltage in hypothyroid newborns compared to healthy infants [22]. Additionally, a cross-sectional study demonstrated increased PR and QTc intervals in both overt and subclinical hypothyroidism during aging [23]. It is noteworthy that prolonged PR intervals are associated with an increased risk of atrial fibrillation (AF) [24].

While our study revealed a consistent trend of prolonged PR and QT intervals in FH rats, a human study investigating infants with severe hypothyroidism found a lower heart rate and QTc interval at one month of age [25]. Notably, no significant differences in PR or QT intervals were observed between these infants and a control group. However, it's crucial to note that this human study focused on newborn infants, unlike our study which examined young and middle-aged rats. These discrepancies might stem from inconsistencies in the results. The ECG changes observed in this study align with the findings of Ghanbari et al., who reported reduced tolerance to ischemic reperfusion in adult rats with fetal hypothyroidism [11]. However, other studies have shown cardioprotective effects of hypothyroidism, attributed to increased protein kinase Cε (PKCε) expression and reduced activation of p46 and p54 c-jun N-terminal kinases (JNKs) in response to ischemic reperfusion [26, 27]. These contrasting findings suggest that variations in gene expression might contribute to the differences in outcome. Further research is needed to investigate the expression of PKCε and JNKs activity in the context of fetal hypothyroidism.

Furthermore, aging is known to be associated with structural and functional heart disorders [28]. This study observed more pronounced ECG changes in the offspring of mothers with fetal hypothyroidism, particularly as they aged, even after restoring euthyroidism. Therefore, maternal hypothyroidism may have a lasting impact on cardiovascular function in their offspring, especially as they get older.

Newborn and young fetal hypothyroid rats exhibited lower body weights compared to the control group, consistent with the findings of Kajantie et al. [29]. A growing body of research suggests a correlation between low birth weight and an increased risk of cardiovascular disease in adults [30, 31].

Due to limitations in laboratory facilities, we were unable to record electrocardiograms in newborn mice. However, this limitation does not diminish the significance of our findings, which demonstrate the impact of congenital hypothyroidism on the electrocardiogram of mice born to mothers with hypothyroidism.

Our study concludes that mothers with hypothyroidism during pregnancy give birth to offspring with lower birth weights, possibly increasing their risk of cardiovascular disease in adulthood due to alterations in ECG values.

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Disclosure of conflict of interest

None.

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