Electrocardiography in Wistar Rat Experimental Model: Analysis and Characterization

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***Abstract*—The experimental model of Wistar rat (WR) is widely used by the scientific community for the evaluation of xenobiotics and environmental stressors. However, in spite of its great use, few publications have explicitly reported the differences between the parameters obtained from the ECG delineation and the different variables involved in the settings of a Wistar rat experiment. Variables such as supplied anesthesia, sex, age, weight, movement restriction and lead used influence the electrocardiographic parameters analyzed, such as RR, QT, PR intervals, P and QRS durations and peak amplitudes of P, Q, R, S, and T-waves.**

The first specific objective of this work is to organize the electrocardiographic parameters that have already been published by the scientific community according to their experimental setup. The second specific objective is to provide new parameters, such as the JTend and Tpe intervals, to the state of the art of Wistar rat ECG characterization. For this purpose, a database of 48 Wistar rats categorized by sex and age, measured in lead II, was processed and delineated.

***Resumen*— El modelo experimental de rata Wistar es ampliamente utilizado por la comunidad científica para la evaluación de xenobióticos y estresantes ambientales. Sin embargo, a pesar de su gran uso, pocas publicaciones han reportado explícitamente las diferencias entre los parámetros obtenidos del delineamiento del ECG para las distintas variables que intervienen en la configuración de un experimento con rata Wistar. Variables como la anestesia suministrada, el sexo, la edad, el peso, la restricción del movimiento y la derivación utilizada influyen significativamente en los parámetros electrocardiográficos analizados, tales como, los intervalos RR, QT y PR, las duraciones P y QRS, y las amplitudes pico de las ondas P, Q, R, S y T.**

El primer objetivo específico de este trabajo es organizar los parámetros electrocardiográficos que ya han sido publicados por la comunidad científica según su *setup* experimental. El segundo objetivo específico es aportar nuevos parámetros, como los intervalos JTend y Tpe, al estado del arte de la caracterización del ECG de rata Wistar. Para ello, una base de datos de 48 ratas Wistar categorizadas por sexo y edad, medida en la derivación II, fue procesada y delineada.

I. Introduction

The experimental model of Wistar rat (WR) is used in several researches on cardiotoxicology and cardiovascular diseases. In the toxicology field, the WRs are used to induce them pathologies or cardiovascular disorders by xenobiotics. This is done, for example, to evaluate the cardiovascular effect of veraniclina [1], the impact of isoprenaline and caffeine on cardiac geometry (hypertrophy) [2], the effect of atropine and propanolol in heart rate variability [3] and the effect of cyclosporin in the electrocardiographic profile [4], among others. On the other hand, environmental stressors such as exposure to air pollution, diet and hypoxia have been studied to evaluate initiation and progression of cardiovascular diseases. For example, the effects of atmospheric carbon monoxide exposure in WRs [5] [6], ECG changes in obese rats [7] and the effects of systemic hypoxia with different levels of CO_2 on RR interval [8]. Besides, WRs have been used as models of myocardial infarction by coronary occlusion [9] [10]. In all cases, the analysis of ECG parameters such as RR, QT and PR intervals are used to evaluate the results of experiment and elucidate mechanisms of action.

The use of WRs model in experimental researches is very common and have increased in the last decades. The WRs provided advantages over other species such as dogs, Guinea pigs and rabbit. The WRs are smaller and consequently much easier and less expensive to handle, they also have less interindividual variability than dogs, are available as transgenic models to evaluate diverses experiments, are widely available in large numbers enabling in depth study and have less potencially confounding preexisting disease [11].

Several experimental setups of WRs have been developed by the scientific community. Konopelski et. al [12] have shown differences between heart rate (HR), PR interval, QRS duration and QT interval that depend on anesthesia supplied to WRs such as pentobarbital, urethane, light ether and ketamine and xylazine. Mutiso et. al [7] have proven that weight afects the ECG parameters in a experiment with overweight WRs. Moreover, Machida et. al [13] have analized WRs with one and three months old and have found differences between amplitudes and intervals in ECG of WRs evidencing the role of the age in ECG parameters. Pereira-Junior et. al [14] have developed an experimental setup for adquisition of ECG in conscious WRs with restrained movement while Damasceno et. al [15] and Tontdo-

nati et. al [16] have implanted electrodes to measure lead II in conscious and unrestrained WRs, evidencing differences between restrained and unrestrained rats.

The aim of this work is to analyze and extend the state of art of the characterization of ECG parameters in WR experimental models.

II. Materials and Methods

A. Wistar rat database

The database was acquired at the Institute of Medical Research Dr. Alfredo Lanari that belongs to the University of Buenos Aires, Argentina. The database has 48 ECG of WRs, separated in different groups: 3 female 2-7 weeks old ($88 \pm 3\ g$), 3 male 2-7 weeks old ($100 \pm 1\ g$), 7 female 7-17 weeks old ($219 \pm 15\ g$), 13 male 7-17 weeks old ($319 \pm 83\ g$), 15 female 17-45 weeks old ($315 \pm 40\ g$) and 7 male 17-45 weeks old ($541 \pm 25\ g$).

Ketamine ($75\ mg/kg$) and Rompun ($0,75\ mg/kg$ xylazine) has been supplied to WRs as anesthesia to record the ECG. All ECG signals have been measured in leads I, II, V1, V3 and V6 for approximately during 5 minutes. Nevertheless, this work only reports the lead II in order to compare with other works. In Fig. 1 the experimental setup is ilustrated where four electrodes were used to measure bipolar leads (near to: left arm, right arm, left leg and right leg) and three precordial leads located horizontally in the intercostal zone.

Fig. 1. Experimental setup: A Wistar rat (WR) in supine position with 7 electrodes connected.

The ECG signals were recorded with ECCOSUR S.A. equipment (Buenos Aires, Argentina) digitalized with a sampling rate of 1 kHz and 12 bit resolution.

Animals were treated according to Argentina's National Drug, Food and Medical Technology Administration Standards (Regulation 6344/96) and the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Pub. No. 85-23, Revised 1996).

B. Extracting the ECG parameters

We have analyzed ECG WRs with LabChart Pro software [17]. These software has a processor that handles ECG signals from rats and other animal species. First, a bandpass filter in the range of 2-300 Hz was applied to the leads. Then, through automatic R-waves detections, several ECG beats were aligned and a template was generated. Each template was characterized with temporal analysis for the PR, QT, JTend, Tpe intervals, P and QRS durations and P, Q, R, S, T-waves peak amplitudes. Sometimes, P-wave and Tendpoint were difficult to find for the automatic delineation. In these cases, an experienced observer has defined these points from calibrated cursor. Finally, for each group of WRs, each parameter was averaged obtaining a mean and standard deviation.

C. Exclusion and inclusion criteria

ECG signals have been included or excluded in the database depending on its morphology. In Fig. 2 several kind of waveshapes extracted of the database are ilustrated. The first one (from top to bottom) is a normal beat and only this kind of signal has been measured for the extraction of ECG parameters. The other signals were excluded due the difficulty of extrating all ECG parameters.

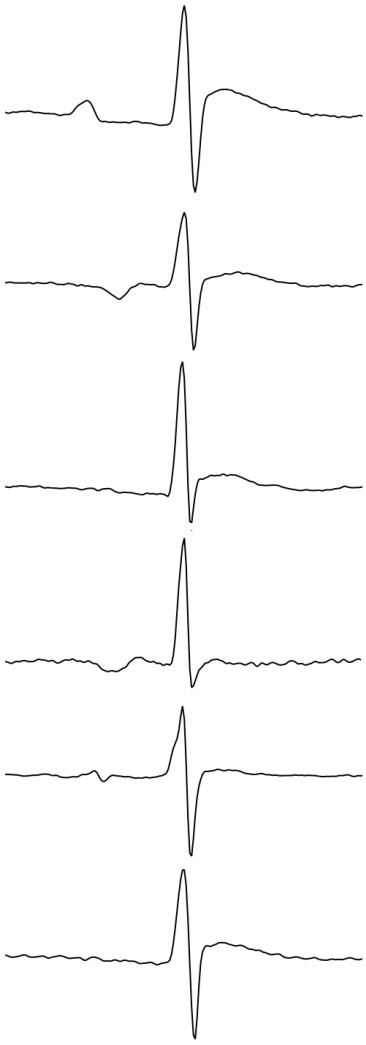

Fig. 2. Differents ECG signals: From top to bottom, normal beat, inverted P-wave and symmetric QRS complex, without P-wave and asymmetric QRS complex, inverted P-wave and asymmetric QRS complex, byphasic P-wave, without P-wave and symmetric QRS complex.

III. Results

Fig. 3 ilustrates the age vs weight curve of our database in which each sex was fitted with an exponential curve. Based on Fig. 3, we have established 2-7 weeks, 7-17 weeks and 17-45 weeks groups in order to classified the WRs.

Table I shows differents experimental settings adopted by several authors. Besides, we have included the experimental setting of this work in order to compare with other authors. Moreover, Table II and Table III shows ECG parameters in the same order that Table I.

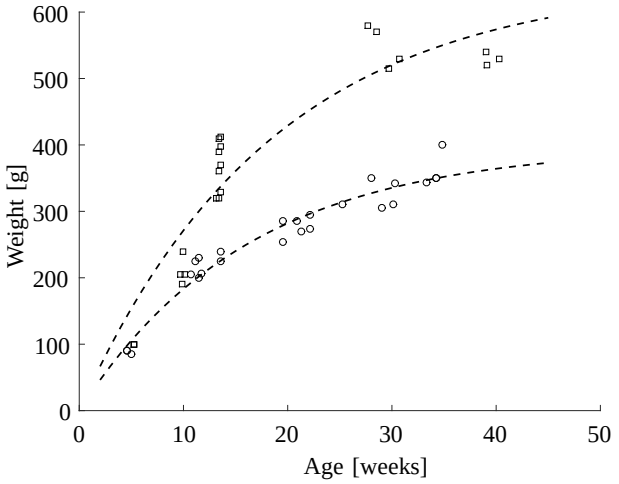

Fig. 3. Age vs weight: the circles represents female WRs and the squares represents male WRs.

IV. Discussion

In order to compare the state of art of WRs ECG parameters with our ECG measurements, the discussion will focus in the most important measurements of each author.

A. RR interval and HR

The RR interval and HR are negative correlated, thus, if RR interval has increased, HR will decrease approximately with the expression $HR \approx \frac{60}{RR}$. Therefore, the comparative analysis is the same for both.

Machida et. al [13] (3 months) and Xu et. al [18] (3 months) have reported similar RR parameter (in this case HR was converted to RR interval using the above HR equation. See Table II) in male WRs under pentobarbital anesthesia. Nevertheless, we have observed (male, 7-17 weeks) a higher RR parameter than the aforementioned values (see Table II) using ketamine and xylazine anesthesia (see Table I). In this way, Konopelski et. al [12] have reported that pentobarbital anesthesia decrease RR interval in comparation with ketamine and xylazine.

On the other hand, Miranda et. al [9] and this work (female, 2-7 weeks) have found coincidence in HR (see Table II) in female WRs under ketamine and xylazine anesthesia, but there is not a weight coincidence as we can see in Table I.

B. PR interval and P duration

Miranda et. al [9] and this work (female, 2-7 and 7-17 weeks) have reported similar PR interval and P duration parameters (see Table II) in WRs under ketamine and xylazine anesthesia. However, Miranda et. al have not reported the age of WRs and the weight is only similar to female 7-17 weeks WRs group (see Table I).

C. QRS complex duration

In order to analize the ventricular repolarization, Tavares et. al [4] and this work (male, 17-45 weeks) have presented similar QRS duration (see Table II) in male adult WRs with same anesthesia (see Table I). However, Tavares et. al have shown a higher HR than this work (male, 17-45 weeks).

Moreover, Buschmann et. al [19] and our results (male, 7-17 weeks) have presented similar QRS duration (see Table II), in spite of the differents anesthesia supplied (see Table I) in agreement with Konopelski et. al [12]. This result could be explained due to QRS duration is not strongly related to the anesthesia supplied.

Finally, Silva et. al [20] and Mutiso et. al [7] have observed very high QRS duration in contrast to the others authors (see Table II).

D. QT interval

In order to study the QT interval, which represent the ventricular depolarization and repolarization jointly, several authors have reported results. For example, Swamy et. al [21] and this work (male, 7-17 weeks) have presented similar QT intervals (see Table II) but Swamy et. al have not reported that kind of anesthesia supplied (see Table I).

Moreover, Machida et. al and this work (male) have not shown strong variation in QT interval for distinct aged.

Besides, Silva et. al [20] have reported very high QT interval and, consecuently, a very low HR (see Table II).

E. JTend and Tpe interval

No authors has reported JTend or Tpe intervals to comparate with our results (see Table II).

F. P-wave peak amplitude

Fraser et. al [22] and this work (male, 7-17 weeks) have reported similar P-wave peak amplitude (see Table III) using dissimiler anesthesia (see Table I).

Moreover, Machida et. al [13] and the present work (male, 2-7 and 7-17 weeks) have observed similar P-wave peak amplitude (see Table III), also using various anesthesia (see Table I), showing a negative correlation between P-wave peak amplitude and aged until WRs 17-45 weeks old.

G. Q-wave peak amplitude

Due to the small or lack of Q-wave in WRs, only Mutiso et. al [7] and our work have measured values of Q-wave peak amplitude (see Table III).

Our results have shown a negative correlation between the absolute value of Q-wave peak amplitude and aged in both sexes. Nevertheless, Mutiso et. al have not reported the same relation in WRs with 7 weeks of difference old (see Table III).

H. R-wave peak amplitude

Fraser et. al [22], Machida et. al [13] (1 month) and our work (male, 2-7 weeks) have observed similar R-wave peak amplitude (see Table III) under distinct anesthesia supplied in the three cases (see Table I).

Also, Machida et. al (3 months) and this work (male, 7-17) have reported similar R-wave peak (see Table III) showing a negative correlation between R-wave peak and aged.

TABLE I
DIFFERENTS EXPERIMENTAL SETTINGS BY AUTHOR. IF SOME SETTING WAS NOT SPECIFIED, WE HAVE INDICATED WITH NR (NON-REPORTED).

	n	Lead	Anesthesia	Sex	Age	Weight
Fraser et. al (1967)	100	II	Light ether	Male	NR	150-255
Buschmann et. al (1980)	6	II	Urethane	Male	NR	330-370
Machida et. al (1990)	5	II	Pentobarbital	Male	1 months	92±1
	5	II	Pentobarbital	Male	3 months	410±14
Tavares et. al (2002)	8	II	Ketamine and Xylazine	Male	Adult	300-400
Miranda et. al (2007)	39	II	Ketamine and Xylazine	Female	NR	173-227
Pereira-Junior et. al (2009)	6	II	Concisous	Male	NR	330-370
Xu et. al (2010)	11	II	Pentobarbital	Male	3 months	250-350
	11	II	Pentobarbital	Male	9 months	550-750
Silva et. al (2010)	10	NR	Pentobarbital	NR	3 months	404,46±9,3
Swamy et. al (2013)	6	NR	Yes	Male	NR	150-200
Mutiso et. al (2014)	20	II	Ketamine	Male	NR	214.7±9.96
	20	II	Ketamine	Male	NR+7 weeks	229,2±7,26
Selcuk et. al (2015)	5	NR	Yes	NR	10-12 weeks	320-360
	5	NR	Yes	NR	10-12 weeks	260-380
This work (2017)	3	II	Ketamine and Xylazine	Female	2-7 weeks	88±3
	3	II	Ketamine and Xylazine	Male	2-7 weeks	100±1
	7	II	Ketamine and Xylazine	Female	7-17 weeks	219±15
	13	II	Ketamine and Xylazine	Male	7-17 weeks	319±83
	15	II	Ketamine and Xylazine	Female	17-45 weeks	315±40
	7	II	Ketamine and Xylazine	Male	17-45 weeks	541±25

TABLE II
ECG TEMPORAL PARAMETERS. IF SOME SETTING WAS NOT SPECIFIED, WE HAVE INDICATED WITH NR (NON-REPORTED).

	RR (ms)	HR (bpm)	PR (ms)	P (ms)	QRS (ms)	QT (ms)	JTend (ms)	Tpe (ms)
Fraser et. al (1967)	NR	334±44,3	65±13	NR	23±5	66±9	NR	NR
Buschmann et. al (1980)	NR	395±38	51±3,5	NR	15±0,8	NR	NR	NR
Machida et. al (1990)	113,4±2,0	NR	46,6±1,3	NR	12±0,4	61,2±0,7	NR	NR
	153,4±6,2	NR	51,4±0,7	NR	13±0,4	62,6±3,0	NR	NR
Tavares et. al (2002)	NR	444,0±15,0	55,0±2,9	27,5±2,0	20	57,5±2,5	NR	NR
Miranda et. al (2007)	NR	277±35	48±9	26±8	21±4	85±10	NR	NR
Pereira-Junior et. al (2009)	149,88±1,21	NR	NR	NR	NR	NR	NR	NR
Xu et. al (2010)	NR	371,3±16,6	49,6±2,4	26,5±1,6	26,4±1,9	96,2±3,5	NR	NR
	NR	338,3±14,8	51,3±1,2	33,9±1,1	27,1±0,9	98,6±4,6	NR	NR
Silva et. al (2010)	NR	186,46±8,53	NR	NR	92,57±5,42	210,14±8,55	NR	NR
Swamy et. al (2013)	NR	471,1±8,59	46,67±1,67	NR	NR	70,83±1,54	NR	NR
Mutiso et. al (2014)	180±7	342±12	30±2,0	28±2,0	81±4,1	105±3,6	NR	NR
	198±81	313±13	26±1,9	25±1,9	77±3,6	102±5,2	NR	NR
Selcuk et. al (2015)	NR	307,2±73,3	43,6±3,58	NR	34,8±1,1	72,8±2,68	NR	NR
	NR	272,8±42,29	42,8±17,9	NR	34,8±1,1	74,8±2,68	NR	NR
This work (2017)	221.3±5.9	271.3±7.4	57.4±12.4	25.4±5.2	17.3±2.3	81.9±14.0	64.6±11.7	52.3±7.7
	219.2±9.6	274.1±11.7	50.9±3.3	26.1±2.2	16.7±2.1	88.6±3.6	72.0±1.9	56.3±4.0
	250.9±14.1	239.8±13.5	50.6±4.3	22.1±3.0	18.3±4.3	81.3±6.9	63.0±7.9	49.4±7.2
	231.6±14.0	259.9±15.3	50.2±3.9	23.7±3.9	16.2±1.8	78.3±4.6	62.2±4.8	51.8±5.5
	282.2±19.6	213.6±15.3	55.1±5.2	22.8±5.1	18.3±2.2	81.9±8.3	63.7±8.5	52.9±9.7
	239.8±16.9	251.3±18.1	63.7±3.2	27.1±5.4	20.7±2.1	87.5±5.4	66.8±6.1	48.3±19.6

Moreover, Miranda et. al [9] have shown a very high value of R-wave peak amplitude and Mutiso et. al [7] have reported a very low value (see Table III).

I. S-wave peak amplitude

Fraser et. al [22] have observed a positive deflection of S-wave (see Table III). In our investigation, S-wave peak was negative in all cases in contrast with Fraser et. al.

Besides, Machida et. al [13] and this work (male) have shown a negative correlation between aged of WRs and S-wave peak amplitude in absolute value but have not reported similar values.

Finally, again Mutiso et. al [7] have observed very low values and have not reported a negative correlation.

J. T-wave peak amplitude

In order to compare the T-wave peak amplitude, we have observed that Machida et. al [13] (1 months), Fraser et. al [22] and our results (male, 2-7 weeks) have reported similar T-wave peaks amplitude (see Table III) in spite of that the three authors have supplied distinct anesthesia such as pentobarbital, light ether and ketamine and xylazine (see Table I).

V. CONCLUSION

Based on results, we have observed several ECG parameters in agreement with our ECG measurements. Nevertheless, the most authors have reported few parameters and have not reported the complete experimental setting. In this sense, we have provided several ECG parameters in three age ranges and both sexes using ketamine and xylazine anesthesia supplied. Besides, we have showed differents kind of possible waveshapes in lead II in contrast with others authors that have not reported the ECG-waves morphology. In other words, we have provided ECG parameters under well established experimental conditions.

TABLE III
ECG AMPLITUDE PARAMETERS. IF SOME SETTING WAS NOT SPECIFIED, WE HAVE INDICATED WITH NR (NON-REPORTED).

	P (μV)	**Q (μV)**	**R (μV)**	**S (μV)**	**T (μV)**
Fraser et. al (1967)	72±46	NR	920±260	330±150	190±66
Buschmann et. al (1980)	NR	NR	NR	NR	NR
Machida et. al (1990)	128±5	NR	770±60	-440±5	190±10
	64±10	NR	420±40	-150±20	90±10
Tavares et. al (2002)	NR	NR	NR	NR	142±25
Miranda et. al (2007)	75±24	NR	1466±199	NR	NR
Pereira-Junior et. al (2009)	NR	NR	NR	NR	NR
Xu et. al (2010)	NR	NR	NR	NR	NR
	NR	NR	NR	NR	NR
Silva et. al (2010)	NR	NR	NR	NR	NR
Swamy et. al (2013)	NR	NR	280±10	NR	NR
Mutiso et. al (2014)	19,8±1,9	-11,2±1,4	71,7±9,0	-20,8±2,1	15,9±1,4
	13,9±1,5	-12,8±1	61,3±8,4	-28,4±4,5	18,8±1,4
Selcuk et. al (2015)	NR	NR	NR	NR	NR
	NR	NR	NR	NR	NR
This work (2017)	163.6±37.8	-33.3±21.9	768.8±172.2	-581.1±33.0	264.2±96.8
	120.5±16.5	-31.3±9.7	806.7±138.7	-564.2±298.6	205.8±60.1
	62.6±29.2	-22.2±10.0	540.1±141.1	-339.1±169.2	127.9±45.8
	75.1±16.1	-24.8±14.4	547.6±102.2	-328.6±148.7	132.9±31.0
	59.6±37.4	-8.3±20.4	528.1±144.0	-289.0±152.1	131.5±41.3
	81.3±19.4	-0.1±8.3	473.2±174.6	-209.0±64.9	120.2±59.8

On the other hand, several problems exist to delineate the ECG of WRs. The peak values has been poorly reported, specialy Q-wave peak due its low level or absence [11]. Besides, the lack of ST segment difficult the localization of QRSend and consecuently the J-point position. Moreover, several different criteria have been proposed in the literature to define the end of the rodent T wave [17]. In this sense, no standar protocol was developed to establish how delineate the ECG-waves.

Finally, we have concluded that in spite of importance of WRs in several fields such as toxicology, behavior and basic research in cardiovascular diseases, even nowadays do not exist a standar of ECG parameters.

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