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THE RESTING ELECTROCARDIOGRAM OF T. CRUZI-INFECTED RATS (1)

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SUMMARY

A total of 125 rats were infected with the Colômbia strain of **T. cruzi** (2000 parasites/g) shortly after weaning. Of these, 58 survived the acute phase and were used in the present experiment. Twenty eight similar but not infected rats served as controls. All rats were submitted to the resting ECG when they were 6 months old. Classic and 3 precordial leads were employed in order to record the ECG as completely as possible. Electrocardiographic changes similar to those found in human chronic Chagas' heart disease and not previously described in this model were found in 44% of the **T. cruzi**-infected rats: left axis deviation (22%), right axis deviation (7%), lengthened and bizarre QRS complex (14%) and abnormal J point elevation (3%). On the basis of these results, we believe that the resting ECG constitutes a valuable tool for studying experimental chronic Chagas' heart disease in rats.

KEY WORDS: Chagas' cardiomyopathy; Trypanosomiasis — South American; Electrocardiography.

INTRODUCTION

It has been stated that an experimental model for studying chronic Chagas' cardiomyopathy should reproduce the hallmark electrocardiographic changes spontaneously occurring in human chronic Chagas' heart disease [22]. These changes have been found in dogs [3,4,12,13], rabbits [20] and occasionally primates [8]. However, electrocardiographic recordings have been rarely obtained in experimental chronic Chagas' heart disease of the rat. An extensive review of the literature has disclosed only one paper in which the resting ECG of **T. cruzi**-infected rats was recorded [18]. Only nonspecific alterations concerning the morphology of the QRS complex were detected, whereas severe AV blocks, bundle branch blocks or fascicular blocks were not observed.

During the last four years were have routinely obtained electrocardiographic tracings from **T. cruzi**-infected rats which are being utilized in experiments concerning the pathogenesis of chronic Chagas' cardiomyopathy. At first, we used only lead (VI) and injected ajmaline to induce ECG changes in some **T. cruzi**-infected rats[16]. Later, we also used precordial and classic leads [6]. Sometimes, before the ajmaline test, we observed ECG changes consistent with myocardial damage which had not been previously described in this model. Therefo-

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re, the present study was performed in an attempt to characterize such electrocardiographic changes and to determine the resting ECG of the T. cruzi-infected rat.

MATERIAL AND METHODS

ANIMALS. A total of 125 male albino rats (Wistar) were infected intraperitoneally with **T. cruzi**, Colômbia strain, 2000 parasites/g, shortly after weaning. During the first month after infection, a blood sample was drawn once a week from the tail of each animal and examined under light microscopy to detect circulating parasites. The animals were kept in groups of 5 to a cage and had free access to water and rat chow. Twenty-eight similar animals not infected with **T. cruzi** served as controls. All rats were maintained under the same environmental conditions during the experiment. Only 58 infected animals which survived the acute phase of the disease were included in the study.

ECG Tracings. An electrocardiograph (ECG 3-FUNBEC) was modified to record at a paper speed of 100 mm/sec and at 2N amplitude. The original electrodes were replaced with five small 1-cm long needles which were introduced into the subcutaneous tissue of the animals. All recordings were made when rats were 6 months old. The animals were first submitted to light ether anesthesia and then injected with 20% urethane (100 mg/kg) into the intraperitoneal cavity. About 15 minutes later the animals were usually pronounced anesthetized and were laid on their backs on a Faraday's cage. This device, as well as the electrocardiograph, were linked to a properly grounded Copperweld's bar. Classic and three precordial leads were recorded as follows: VA) the electrode was placed at the 4th right intercostal space at the parasternal line; VB) the electrode was positioned at the 5th left inlar line in the 5th left intercostal space; VC) the electrode was positioned at the 5th left intercostal space in the anterior axillary line. The P wave, PR and QaT interval (measured from the beginning of the QRS complex till the first half of the T wave)[5] were analysed in the VB lead because this was the only one free from electric interference. The QRS, however, could be studied in all leads. Heart rate was determined by the usual method: (1500/n)x4, in which n is the number of mm between two successives R waves. The QRS axis was determined as previously described[11].

STATISTICAL ANALYSIS. The values of these electrocardiographic parameters did not have normal distribution, so that it was not possible to establish the confidence intervals for each electrocardiographic parameter. Thus, the 5th and 95th percentiles were determined for each parameter. Values higher than 95th + 10% 95th or lower than 5th — 10% 5th were arbitrarialy considered to be abnormal. Left axis deviation was diagnosed when the QRS axis was beyond — 45.°, whereas right axis deviation was detected when the QRS axis was beyond + 120.°. Lengthening of the QRS complex was detected when there were at least 2 derivations in which the QRS complex was greater than the 95th + 10% 95th percentile cited above. J point elevation > 1 mm in the I and/or AVL and/or VC leads was considered to be abnormal. These patterns have not been observed in normal rats[9,10,14,19].

RESULTS

CONTROL RATS — The tracing obtained consisted of a P wave followed by a PR interval, followed in turn by a QRS complex. Several problems, however, arose with respect to T wave termination, all of them related to the difficulty in establishing the final portion of its inscription. A true ST segment was not observed in any tracing. Qr complexes were seen in the VA lead in 24 out of 28 tracings (85%). A rudimentary Q wave was detected in 1 out of 28 recordings (3%) in the I and AVL leads. Unremarkable J point depression was observed in the I and AVL leads in almost all leads. Neither axis deviation nor J point elevation was detected. The values of each eletrocardiographic parameter as well as the 5th and 95th percentiles are summarized in table 1 and illustrated in figure 1,A.

INFECTED RATS — Several electrocardiographic abnormalities were detected in these animals. Marked left axis deviation was obser ved in 13 of 58 tracings (22%). Right axis deviation with a deep S wave in the II, III and AVF leads was seen in 4 out of 58 tracings (7%). A lengthened and bizarre QRS complex

TABLE I

Value of each electrocardiographic parameter and its respective 5th and 95th percentiles

			$\bar{x}$	SD	5th	95th
	HR	(bpm)	406	57	337	496
	P	(ms)	17.50	1.1	15.00	19.50
	PR	(ms)	49.00	5.0	40.59	60.40
	QRS	(ms)	20.47	2.4	17.53	25.37
I	R	(mv)	0.47	0.2	0.16	0.79
	S	(mv)	0.11	0.0	0.03	0.28
	QRS	(ms)	21.24	3.1	17.70	27.25
II	R	(mv)	0.51	0.2	0.20	0.85
	S	(mv)	0.17	0.1	0.04	0.37
	QRS	(ms)	20.26	2.9	15.80	24.39
III	R	(mv)	0.23	0.1	0.02	0.68
	S	(mv)	0.17	0.1	0.08	0.42
	QRS	(ms)	21.51	3.1	16.93	27.19
aVR	R	(mv)	0.10	0.0	0.19	0.85
	Q	(mv)	0.48	0.2	0.01	0.27
	QRS	(ms)	20.08	3.9	15.10	28.09
aVL	R	(mv)	0.27	0.1	0.13	0.65
	S	(mv)	0.09	0.1	0.00	0.37
	QRS	(ms)	19.80	3.1	16.14	23.43
aVF	R	(mv)	0.30	0.1	0.08	0.57
	S	(mv)	0.12	0.0	0.04	0.29
	QRS	(ms)	20.92	2.9	16.64	25.15
VA	R	(mv)	0.08	0.0	0.07	0.54
	Q	(mv)	0.26	0.1	0.02	0.19
	QRS	(ms)	21.56	3.1	17.57	28.35
VB	R	(mv)	0.58	0.2	0.22	0.94
	S	(mv)	0.13	0.0	0.00	0.23
	QRS	(ms)	19.72	2.5	15.60	24.95
VC	R	(mv)	0.25	0.1	0.09	0.54
	S	(mv)	0.04	0.0	0.00	0.15
	QRS	axis (')	29	27.5	—16.39	—67.94
	QaT	(ms)	32.66	5.7	23.54	41.07

HR — heart rate. $\bar{x}$ = mean; SD = standard deviation; mS = milliseconds; mV = millivolt; P = P wave; PR = PR interval; QRS = QRS complex; R.S.Q = amplitudes of these waves; QaT = QaT interval; (') = degrees

in at least two leads was observed in 9 of 58 recordings (14%). Abnormal J point elevation in the I, AVL and VC leads could be demonstrated in 2 of 58 tracings (3%). The same rate was obtained with respect to ventricular premature contractions. These findings are given in table 2 and illustrated in figure 1,B and figures 2,A,B,C.

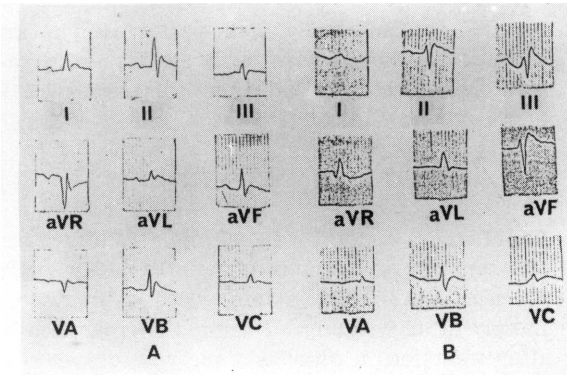

Figure 1

A. ECG tracing from a control rat showing a Qr pattern in the VA lead and absence of the ST segment.

B. ECG tracing from a T. cruzi-infected rat showing a lengthened and bizarre QRS complex in the I and VC leads.

TABLE II

Electrocardiographic abnormalities detected in T. cruzi-infected rats

ECG	Animals (n=58)	Percentage
Right axis deviation	4	7
Left axis deviation	13	22
Lengthened QRS complex	9	14
Abnormal J point elevation	2	3
Ventricular premature contractions	2	3

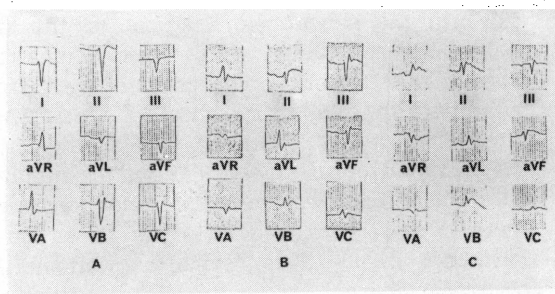

Figure 2

A. ECG tracing showing marked right axis deviation consistent with right ventricular hypertrophy. (T. cruzi-infected rat).

B. ECG tracing displaying left axis deviation, indicating left anterior hemiblock. (T. cruzi-infected rat).

C. ECG tracing obtained from a T. cruzi-infected rat exhibiting an abnormal J point elevation in the I, VB and VC leads.

DISCUSSION

CONTROL RATS — The resting ECGs obtained for control rats essentially confirmed results previously reported for these animals [9,10,14,19]. The most relevant feature of the resting ECG of rats and other small mammals

is the absence of the ST segment [14]. The other electrocardiographic parameters resemble those found in human electrocardiograms. Nonetheless, slight J point depression in the I and AVL leads is usually found [14]. In rats, electrocardiographic recordings obtained from the left parasternal border up to the anterior axillary line are very similar [10]. On some occasions, a slight J point elevation can be observed in the lead corresponding to the human V2, but never in the VC or AVL or I lead [10]. All these characteristics were seen in our experiment. The derivation corresponding to the human V1 lead (called VA lead in the present experiment) has been seldom recorded. In this study, we observed a Qr pattern in the VA lead of 85% of the control rats. In human electrocardiography, this pattern is consistent with myocardial disease [21]. These alterations have not been previously described in the few electrocardiographic studies previously performed on these animals. It is conceivable that such a change is related to the forces of ventricular activation, which depend on the basal region of the right ventricle facing the homolateral shoulder. Nonetheless, only vectorcardiographic studies could adequantely account for this finding.

INFECTED RATS — In this experiment, 44% of **T. cruzi**-infected rats showed ECG changes which have not been previously demonstrated. These alterations are thought to be consistent with chronic myocardial damage. Marked left axis deviation suggesting left anterior hemiblock was the abnormality most often detected. The present frequency of this alteration was similar to that found in human chronic Chagas's heart disease [13]. Left axis deviation has been demonstrated in senescent rats (800 days old) and has been related to severe myocardial fibrosis [7]. Similarly, it has been demonstrated that fibrosis in the conduction system does occur in patients with left anterior hemiblock [2]. Therefore, we postulated that the left axis deviation found in our rats was the consequence of myocardial injury. Right axis deviation suggesting right ventricular hypertrophy (basal regions) could be observed in 7% of the infected animals. Nonetheless, there was no evidence of an electrocardiographic pattern indicating right bundle branch block, the most frequent abnormality seen in human chronic Chagas' heart disease [13]. Undoubtedly, the absence of such a pattern was due to the peculiarity of the conducting system of rats in which the right bundle branch is very hypoplastic, with no electrophysiological significance [17]. A lengthened QRS complex indicating intraventricular conduction disturbances was detected in 14% of these animals. It has been demonstrated that lengthening of the QRS complex is due to intramyocardial fibrosis [15]. Thus, we believe that this feature is related to chronic myocardial damage. Abnormal J point elevation was observed in 3% of the rats. ANSELMI et al. [4] have detected this alteration in dogs chronically infected with **T. cruzi.** The following morphologic changes were detected by means of an electrode placed on the epicardial surface of the corresponding region: thinning of the myocardium, chronic myocarditis and fibrosis. Therefore, this electrocardiographic change can also indicate myocardial injury. Ventricular premature contractions were detected in 3% of the **T. cruzi**-infected rats. This fact may have been the consequence of the short duration of the ECG tracing or of the lack of continuous 24h electrocardiographic monitoring.

In our view, the electrocardiographic changes observed in this investigation may have been due either to the methodology employed or the Colômbia strain used. REVELLI and associates [18] recorded only two precordial leads (V2 and V5), which have been shown to produce a similar electrocardiographic pattern in the rat electrocardiogram [10] in contrast to that observed in human ECG. Therefore, the right precordial lead which is important to characterize, for example, right ventricular hypertrophy or intraventricular conduction delay at the right bundle branch, might be overlooked. However, since the pattern suggestive of right ventricular hypertrophy was detected only in 7% of animals, and right bundle branch block is not usually observed in the rat electrocardiogram, we must admit that the methodology employed by us does not represent the best explanation for our results. It is known that the Colômbia strain of **T. cruzi** has low virulence but high pathogenicity. The myocarditis induced by this strain can be severe [1]. In the study by REVELLI et al. [18] the strain employed did not have the same characteristics as the

Colômbia strain. The Colômbia strain, therefore, appears to be adequate to induce severe myocardial lesions which may be manifested on the electrocardiogram. This fact may account for the disparity between our results and those previously described [18].

CONCLUSIONS — The data obtained in this experiment allowed us to conclude that the resting ECG represents a reliable method for characterizing chronic Chagas' heart disease in **T. cruzi**-infected rats. It is important to emphasize that the electrocardiographic changes seen in 44% of **T. cruzi**-infected rats were similar to those found in human chronic Chagas' heart disease. However, we are aware that the sensitivity, specificity and predictive value of this method remain to be determined We believe that the Colômbia strain is suitable for the study of experimental chronic Chagas' heart disease on the basis of its ability to induce chronic myocarditis. In addition, we feel that the resting ECG used in association with the ajmaline test to reveal concealed chronic Chagas' cardiopathy will provide new perspectives for establishing the rat as an adequate experimental model for chronic Chagas' heart disease.

RESUMO

Caracterização do eletrocardiograma basal de ratos infectados pelo T. cruzi.

Cento e vinte e cinco ratos Wistar foram infectados pelo **T. cruzi**, cepa Colômbia, 2000 parasitas/kg peso corporal, via intraperitoneal, logo após o desmame. Cinquenta e oito animais sobreviveram à fase aguda da infecção e foram utilizados no presente experimento. Vinte e oito animais semelhantes mas não infectados serviram como controles. O eletrocardiograma basal de cada animal foi registrado quando o rato estava com 6 meses de idade. Para tanto, utilizamos 3 derivações précordiais bem como as derivações clássicas a fim de obtermos o mais completo ECG basal possível. Alterações eletrocardiográficas semelhantes às encontradas na Cardiopatia Chagásica Crônica humana, que não tinham sido descritas previamente neste modelo, foram observadas em 44% dos ratos infectados pelo **T. cruzi:** Desvio do SÂQRS à esquerda (22%), desvio do SÂQRS à direita (7%), complexo QRS bizarro e/ou alargado (14%), supradesnivelamento do ponto J (3%). Com base nestes resultados, acreditamos que o ECG basal constitui importante metodologia para o estudo da Cardiopatia Chagásica Crônica experimental do rato.

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