PREVENTION OF ELECTROCARDIOGRAPHIC AND HISTOPATHOLOGIC ALTERATIONS IN THE MURINE MODEL OF CHAGAS' DISEASE BY PREINOCULATION OF AN ATTENUATED TRYPSANOSOMA CRUZI STRAIN

Carlos Alberto CUNEO (2), Emma MOLINA DE RASPI (2), Miguel Angel BASOMBRIO (2)

SUMMARY

The effects of infection with Trypanosoma cruzi on the electrocardiographic tracings of mice were studied in 4 groups of animals: (1) normal; (2) infected with a pathogenic T. cruzi strain (TS COB); (3) immunized with 3 intraperitoneal inocula of 10^6 attenuated T. cruzi epimastigotes (TCC) and (4) immunized-infected, which sequentially received the treatments of groups 3 and 2. Infection and protection were confirmed by xenodiagnosis and histopathology. Isolated alterations such as extrasystolia, 1st degree atrioventricular block, arrhythmia and ST elevation were observed in normal as well as infected mice. However, tracings taken repeatedly on each mouse over a 293 day period revealed a set of alterations which were more frequently seen in infected (14/22) than in normal (4/27) animals (p = 0.00048). These alterations consisted of supraventricular tachycardia, sinus bradycardia and persistent, first degree AV blocks, often associated to pacemaker changes. Inoculation of attenuated T. cruzi (group 3) did not increase these alterations (2/27 mice) but significantly prevented their development after challenge with the pathogenic strain (1/19 versus 14/22 mice, p = 0.000095). Thus, preimmunization reduced not only parasiteemia but also a pathogenic consequence of T. cruzi infection. This evidence is relevant for immunoprevention studies against Chagas' disease.

KEY WORDS: Chagas' disease; Electrocardiogram; Histopathology; Heart; Immunization.

INTRODUCTION

Electrocardiographic (ECG) abnormalities, with or without accompanying clinical symptoms, are the most frequent finding in Chagas' disease. Several animal models have been explored in order to reproduce these alterations. Mice should be more suitable than larger animals to bring ECG alterations into context with infection or immunity to Trypanosoma cruzi. Host-parasite interactions have been extensively explored in mice and these animals can economically be used in large numbers.

We have previously studied the immunization against chronic T. cruzi infection in mice by parasitological, histopathological and serological determinations. Moreover, our studies on the mouse ECG allowed us to characterize some T. cruzi-associated ECG alterations, particularly those related to atrioventricular conduction.

The purpose of this work was to depict the ECG alterations which distinguish normal from...
chagasic tracings and to see whether such alterations can be prevented by immunization against T. cruzi.

MATERIAL AND METHODS

Mice. Swiss male mice were used. They weighed 21 ± 2g at the beginning and 52 ± 5g at the end of the experiments. Hearts weighed at this time 230 ± 61mg.

Parasites. An attenuated and a virulent strain of T. cruzi were used for immunization and challenge respectively. The attenuated strain, named TCC has been kept in culture for more than 16 years. During this period, a progressive loss of in vivo infectivity along with adaptation to in vitro growth was detected. The parasites were subcultured every 2 weeks in glass bottles with biphasic, liver-heart infusion medium and antibiotics. Most parasites were in the epimastigote stage, with less than $10^3$ trypomastigotes. No histopathologic lesions were detected after inoculation of these parasites in mice.

The virulent isolate (TS COB) was obtained from one Triatoma infestans captured in a human dwelling in Cobos, Province of Salta, Argentina. This isolate induces typical lesions of Chagas’ disease in at least the heart, muscle and urinary bladder of mice.

Xenodiagnosis. Groups of 10, third instar T. infestans were fasted for one month and then allowed to feed on each anesthesized experimental animal for 20 minutes in darkness. Thirty and sixty days later, a fresh mount of the pooled bug’s feces diluted in culture medium was examined under the microscope in over 200, 0.45mm diameter fields.

Electrocardiograms. ECG tracings were taken from each mouse under sodium pentobarbital anesthesia (50mg/Kg) at various times post challenge. Clamp-type electrodes were connected to each limb after moistening the skin with 96% alcohol and 0.9% Na Cl solution. This provided electric contact and harmless immobilization of the animal. DI, DII, DIII, a VR, a VL, a VF, two precordial and one subxifoid lead tracings were recorded on a Fukuda Denshi electrocardiograph with paper speed set at 50 mm/sec and amplitude at 20mm/mV.

Diagnostic criteria. Normal heart rate: 486 ± 83 beats per minute. Sinus bradycardia: sinus rhythm less than 403 beats per minute. First degree auriculo ventricular (A-V) block: heart rate multiplied by PQ interval exceeding 23.8 (see ref. 8). Supraventricular extrasystolia: premature beats with or without P wave and normal QRS shape. Supraventricular tachycardia: three or more supraventricular premature contractions in a run.

Histopathology. The heart, urinary bladder and quadriceps muscle of each mouse were fixed in 10% formaldehyde and histological, hematoxilin-eosin stained sections were studied. Quantitation of lesions was based on a double-blind analysis of 3 frontal sections of each organ, each taken at approximately 1mm from each other. The degree of inflammatory mononuclear infiltration was classified as follows: 0 — no lesions; 1 — tissues presenting a total of 1 to 4 foci of infiltration in all sections; 2 — more than 4 foci and 3 — extensive or confluent areas of infiltration, often associated with degenerative or fibrotic lesions.

Experimental schedule. Four groups of mice were used. Group 1 (“normal”) consisted of 27 mice which only received injections of culture medium. Group 2 (“infected”, 22 mice) received an intradermal inoculum of 0.05 ml of T. infestans feces diluted in culture medium containing 10 TS COB trypomastigotes. Group 3 (“immunized”, 22 mice) received 3 intraperitoneal injections of 10^6 TCC parasites diluted in 0.1 ml of culture medium at weekly interval. Group 4 (“immunized-infected”, 19 mice) was treated sequentially as groups 3 and 2.

Time schedules were as follows. Mice received the first immunizing inoculum when they were 2 months old and were challenged at 3 months of age (day 0). All animals were subjected to xenodiagnosis on days 27 and 336 and to ECG tracings on days 29, 111, 218 and 322. Autopsies and histopathological study were performed on day 377 on all animals, except for a few which were autopsied as they unexpectedly died during the study.

There was some variation in the number of mice per experimental group that were used for measurement of different parameters. This was due to animals lost during the experiment and to loss of a few samples of triatomae or tissues.
RESULTS

Xenodiagnosis

All mice in the infected group had and active *T. cruzi* infection during the experiments, since either before (day 27) or after (day 336) ECG determination, the parasite was recovered from 100% of the animals by xenodiagnosis. Conversely, no parasites could be recovered by xenodiagnosis from mice inoculated with TCC alone (group 3).

Preinoculations with TCC produced a significant and lasting reduction in the level of parasitemia, as no parasites could be recovered from most mice in the immunized-infected group. Again, this reduction was detected both before (day 27) and after (day 336) the ECG determinations (Table 1).

![Fig. 1 — Hematoxylin-eosin stained section of mouse heart (base of ventricle), 377 days after *T. cruzi* infection. Note a dense lymphomonocytic infiltrate (left) and slight fibrosis between muscle fibers (right).](image)

<table>
<thead>
<tr>
<th>Days post infection</th>
<th>Positive mice / Total mice</th>
<th>p**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immunized-infected mice</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>4/15</td>
<td></td>
</tr>
<tr>
<td>336</td>
<td>3/12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17/17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16/16</td>
<td>0.0000105</td>
</tr>
<tr>
<td></td>
<td>0.000032</td>
<td></td>
</tr>
</tbody>
</table>

* Xenodiagnoses were always negative in mice inoculated with TCC alone (Group 3)
** Calculated with Fisher’s exact test.

Histopathology

Most mice in the infected group had alterations compatible with experimental Chagas’ disease (Fig. 1). Hearts showed interstitial inflammatory infiltrates, often subendocardial, in the atrial wall. The ventricular tissue occasionally presented mononuclear infiltrates, predominating around valves and blood vessels. Localized areas of degenerating fibers were often accompanied by adjacent hypertrophic or peripherally located nuclei. Discrete areas of fibrosis were found in about half of the hearts studied.

There was a sharp association between *T. cruzi* infection and infiltrative heart lesions. Degenerative and fibrotic lesions, on the other hand, appeared to be a consequence of old age, as they were found in normal mice and most animals were autopsied on day 377 post infection.

Urinary bladders presented focal and perivascular mononuclear infiltrates. Skeletal muscle showed the same type of lesions, but they were more extensive and severe, including fiber degeneration and fibrotic scars.

In contrast to the above findings, no histopathological alterations were found in mice of groups 1 (normal) or 3 (TCC alone).

The blind, semiquantitative evaluation of specimens revealed that in the immunized infected group the infiltrative lesions had been prevented, as compared to the infected group (Fig. 2). The differences were significant in heart (p < 0.005), muscle (p < 0.001) and urinary bladder (p < 0.04).

ECG tracings

Some ECG alterations (listed in Table 2, top) were found as often in the infected as in the normal group and could not be associated with *T. cruzi* infection. These were observed in a small proportion of mice and disappeared in subsequent ECG tracings of the same animal. They included extrasystolia and pacemaker
TABLE 2

Screening for ECG alterations associated with *T. cruzi* infection in anesthetized mice

<table>
<thead>
<tr>
<th>Type of alteration</th>
<th>Number of alterations / Total ECG's</th>
<th>Number of alterations / Total mice*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (%)</td>
<td><em>T. cruzi</em> infected (%)</td>
</tr>
<tr>
<td>Supraventricular extrasystolia</td>
<td>3/100 (3)</td>
<td>4/74 (5)</td>
</tr>
<tr>
<td>Pacemaker changes</td>
<td>5/100 (5)</td>
<td>4/74 (5)</td>
</tr>
<tr>
<td>AV block, 1st degree</td>
<td>8/100 (8)</td>
<td>14/74 (19)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>5/100 (5)</td>
<td>10/74 (14)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>0/100 (0)</td>
<td>3/74 (4)</td>
</tr>
<tr>
<td>Total <em>T. cruzi</em>-associated alterations</td>
<td>13/100 (13)</td>
<td>20*/74 (27)</td>
</tr>
</tbody>
</table>

* Because some animals or ECG tracings had more than one alteration, these have not been aggregated in totals.

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Fig. 2 — Evaluation of tissue damage found in immunized-infected (IMM-INF) and infected (INF) groups of mice, 377 days after *T. cruzi* challenge. Lesions were classified blindly according to a predetermined score (See Materials and Methods). *p* values were calculated with the Mann Whitney "U" test.

Changes not associated to AV blocks. The level of the ST segment showed remarkable variation in normal mice.

Another set of alterations (Fig. 3 and Table 2, bottom), consisting of 1st degree AV blocks, supraventricular tachycardia and sinus bradycardia, was found significantly more often in infected (14/22) than in normal mice (5/27, *p* = 0.00136). The diagnosis of these alterations required their finding in the same mouse in 2 or more occasions and they were considered to be associated with *T. cruzi* infection.

Inoculation of TCC alone (group 3) did not produce significant ECG changes as compared to controls (Table 3).

Preinoculations of TCC prevented *T. cruzi*-associated ECG alterations. These were as infrequent in the immunized or immunized-infected groups as in the normal group (Table 3).

Relation between ECG alterations and heart histopathology

Histopathological and electrocardiographic records of the same mouse were obtained in 30 cases from all experimental groups. Microscopic alterations were described as mononuclear infiltrates, hypertrophy and fibrosis. Both hypertrophy and fibrosis were found in normal animals and there was no association between these lesions and ECG alterations or *T. cruzi* infections.

Mononuclear infiltrates, predominating in atria and perivalvular tissues were found exclusively in *T. cruzi* infected mice. They were found in 78% of electrocardiographically abnormal mice and in only 29% of mice with normal ECG (*p* = 0.016, see Table 4).
Fig. 3 — Electrocardiographic tracings of mice. 1: Normal D II tracing. 2: First degree AV block. Note prolonged PR interval as compared to 1. 3: Supraventricular tachycardia. 4: Sinus bradycardia.

**TABLE 3**

Prevention of electrocardiographic alterations in *T. cruzi* infected mice by preinoculation of culture-attenuated parasites (TCC strain).

<table>
<thead>
<tr>
<th>Group</th>
<th>Immunization</th>
<th>Challenge</th>
<th>ECG alterations*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Normal</td>
<td>–</td>
<td>–</td>
<td>4/27</td>
<td>15</td>
</tr>
<tr>
<td>2 Infected</td>
<td>–</td>
<td>$10^2$ TS COB id**</td>
<td>14/22</td>
<td>64</td>
</tr>
<tr>
<td>3 Immunized</td>
<td>$10^6$ TCC ip x 3</td>
<td>–</td>
<td>2/22</td>
<td>9</td>
</tr>
<tr>
<td>4 Immunized-infected</td>
<td>$10^6$ TCC ip x 3***</td>
<td>$10^2$ TS COB id</td>
<td>1/19****</td>
<td>5</td>
</tr>
</tbody>
</table>

* First degree AV block, sinus bradycardia and supraventricular tachycardia.
** Intradermal.
*** Intrapertioneal.
**** Significant reduction as compared to group 2 ($p = 0.000096$).
### TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Total mice</th>
<th>Mice with histopathological alterations in heart number (%)</th>
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<tr>
<td></td>
<td></td>
<td>Infiltration</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Mice with normal ECG or non <em>T. cruzi</em> associated alterations.***</td>
<td>21</td>
<td>6 (29)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Mice with <em>T. cruzi</em> associated ECG alterations.**</td>
<td>9</td>
<td>7 (78)</td>
<td>6 (67)</td>
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<td></td>
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* Most autopsies were performed 377 days after challenge.
** First degree AV block, sinus bradycardia and supraventricular tachycardia.
*** Including supraventricular extrasystolia, pacemaker changes and sinus tachycardia.

### DISCUSSION

The data presented here show that characteristic ECG alterations can be found in a high proportion of mice after infection with *T. cruzi*. Preimmunization of the animals with an attenuated *T. cruzi* strain can prevent these alterations. Parasitological and histological findings on the same animals indicated the presence of chronic infection and disease (group 2) or immunological protection (group 4) during the 293 day period covered by this electrocardiographic study.

Electrical signals from the mouse heart have obviously not been as thoroughly interpreted as those from the human heart on account of the small size and high beat rate of this organ. The data so far available on prevalence and specificity of *T. cruzi*-associated ECG alterations in mice differ among authors and may depend on mouse or parasite strains. There is, however, a general agreement that *T. cruzi* infected mice develop a spectrum of ECG changes and may depend on mouse or parasite strains. There is, however, a general agreement that *T. cruzi* infected mice develop a spectrum of ECG changes and may depend on mouse or parasite strains. There is, however, a general agreement that *T. cruzi* infected mice develop a spectrum of ECG changes and may depend on mouse or parasite strains. There is, however, a general agreement that *T. cruzi* infected mice develop a spectrum of ECG changes and may depend on mouse or parasite strains. 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found in aged, normal mice with no evident ECG alterations. The presence of inflammatory mononuclear infiltrates and possibly focal hyperthrophy, are closely correlated with specific ECG changes such as 1st degree AV block and supraventricular tachycardia.

In view of the numerous evidences for an autoimmune mechanism in T. cruzi induced myocarditis1,7,9, it may seem paradoxical that immunization against the parasite in the mouse model prevents both histopathological and electrocardiographic manifestations of cardiopathy. It is increasingly evident that pathogenic or protective responses are the consequence of sensitizing the host with T. cruzi antigens in two different ways: the first is represented by parasite fractions or partially purified antigens plus adjuvants. These can elicit heart specific autoantibodies, cytotoxic T lymphocytes, myocarditis and/or ECG alterations9,17,18. The second way is represented by live attenuated parasites or flagellar fractions. These do not seem to elicit pathological manifestations10,16 and, most importantly as shown here, they are preventable by a specified immunizing procedure.

The delineation of the antigenic specificities inducing either pathogenic or protective responses is necessary for understanding and eventually preventing heart disease in American Trypanosomiasis. Although these antigens have not been fully characterized so far, the possibility of producing the desired type of response in the mouse model, even by using crude or living immunogens as shown in this work, is a step forward toward that goal.

RESUMO
Prevenção das alterações eletrocardiográficas e histopatológicas em modelo murino de doença de Chagas através da pré-inoculação de cepa atenuada de Trypanosoma cruzi

Os efeitos da infecção do Trypanosoma cruzi nos traçados eletrocardiográficos de camundongos foram estudados em quatro grupos de animais: 1. normal; 2. infectado com cepa patogênea de T. cruzi (TS.COB); 3. imunizados com três inoculações intra-peritoneais de 10⁶ epimastigotas de T. cruzi atenuadas (TCC) e 4. imunizados e infectados, que receberam sequencialmente os tratamentos dos grupos 3 e 2. A infecção e proteção foram confirmadas por xenodiagnóstico e histopatologia. Alterações isoladas tais como extrassistolia, bloqueio de primeiro grau átrio-ventricular, arritmia e elevação do ST foram observados tanto em camundongos normais como infectados. Entretanto, os traçados tomados de maneira repetida em cada camundongo durante um período de 293 dias revelaram conjunto de alterações que foram vistas mais frequentemente em animais infectados (14/22) que nos normais (4/27) (p = 0.00048). Estas alterações consistiram de taquicardia supra-ventricular, bradicardia sinusio, bloqueios de primeiro grau AV, persistentes, frequentemente associadas a alterações do “pacemaker”. A inoculação da cepa atenuada de T. cruzi (grupo 3) não aumentou estas alterações (2/27) mas preveniu de maneira significante o seu desenvolvimento após o desafio com a cepa patogênica (1/19 versus 14/22 camundongos, p = 0.00095). Portanto, a pré-imunização reduziu não somente a parasitemia mas a consequência patogênica da infecção pelo T. cruzi. Esta evidência é relevante nos estudos de imunoprevenção em doença de Chagas.

REFERENCES


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