Adenosine Induces Ventricular Arrhythmias in Hearts With Chronic Chagas Cardiomyopathy

Edilmar Alvarado-Tapias, a Marianna Rivas-Coppola, a Alfonso Alvarado, b María Bello, b Mario Briceño, a Claudia Rodríguez-Bonfant e and Rafael Bonfante-Cabarcas b

aUnidad de Bioquímica, Decanato de Ciencias de la Salud, Universidad Centroccidental Lisandro Alvarado, Barquisimeto, Venezuela
bUnidad de Parasitología Médica, Decanato de Ciencias de la Salud, Universidad Centroccidental Lisandro Alvarado, Barquisimeto, Venezuela

INTRODUCTION

The heart is the main organ affected by Chagas disease. Some 20%-30% of patients suffer chronic chagasic cardiomyopathy (CCC), characterized by heart failure, arrhythmias and sudden death. Microvascular lesions have been implicated in the pathogenicity of CCC; these cause multiple ischemic foci, leading to an increase in the concentration of adenosine, the cardiovascular effects of which are mediated by G protein-coupled receptors.

The therapeutic properties of adenosine have been associated with proarrhythmic effects. In patients with structurally normal hearts, adenosine can induce atrial fibrillation, an increase in atrioventricular (AV) node conduction, and nonsustained polymorphic ventricular tachycardia. In children and adults with prolonged QT syndrome, it can induce torsade de pointes (TM)-type ventricular tachycardia.

Sudden death in Chagas disease is owed to ventricular fibrillation (VF) conditioned by humoral, vascular and structural anomalies. Ventricular fibrillation has been related to ventricular repolarization abnormalities reflected in a long QT interval.
interval and early- (the R-on-T phenomenon) and late-coupled premature ventricular complexes. Focal myocardial ischemia in Chagas disease induces the release of adenosine, which unleashes fatal arrhythmias facilitated by repolarization abnormalities. The present work investigates the role of the adenosinergic system in inducing of ventricular arrhythmia.

METHODS

Sample

Twenty-eight Sprague-Dawley rats were divided into 2 groups: a control group of healthy rats (n=14) and a group with CCC (n=14; confirmed histopathologically to have chronic myocarditis) (Figure 1).

Isolated Heart

A Langendorff continuous retrograde perfusion system was set up, involving a modified Krebs-Henseleit-type solution containing 10 nmol of isoproterenol, pH 7.35-7.45, bubbled with 95% O₂ and 5% CO₂ at 37°C. The isoproterenol was used to maintain high adrenergic tone and to facilitate the appearance of arrhythmias. Electrocardiographic readings were taken in bipolar mode; the electrodes were located at the tip of the right atrium. The effect of adenosine was tested at increasing concentrations (10-3333 µmol). The effects of selective A1 (1,3-dipropyl-8-cyclopentylxanthine [DPCPX]), A2a (8-chlorostyril caffeine [8-CSC]) and A2b (alloxazine [ALLO]) receptor antagonists, and the A3 antagonist VUF 5574, were assayed in the presence and absence of 0.33-1 mmol adenosine.

Data Analysis

Data were analyzed using the Student t test or ANOVA for paired samples as required, followed by the Bonferroni test. Qualitative variables were analyzed using the χ² test. Significance was set at P<.05.

RESULTS

Electrocardiograms were recorded with pentobarbital anesthesia before setting up the Langendorff preparation; these showed chagasic heart rhythm abnormalities (nodal extrasystoles) in five rats, as well as conduction abnormalities (AV and fascicular block). Three control rats showed RR variability only (Figure 1).

Electrocardiographic Variables

Tables 1 and 2 show the PR, QRS and QT intervals obtained with increasing doses of adenosine and with DPCPX in the presence of 333 µmol of adenosine. The results show that adenosine induced an increase in the QT interval that was reverted with DPCPX. No significant differences were seen for the PR and QRS intervals.

Figure 2A shows the increase in the QT interval and the presence of early depolarizations (arrow). Figure 2B shows premature ventricular complexes emerging from the T wave. Figure 2C shows the TP phenomenon emerging from a prolonged T wave.
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Ventricular Fibrillation

Adenosine induced VF in 50% (n=7) of chagasic hearts and 7.14% (n=1) of healthy hearts (Figure 2D). The chagasic hearts were associated with the possibility of fibrillation (P < .05). No VF was seen in the presence of DPCPX and 8-CSC, but 8-CSC induced ventricular tachycardia in 50% (n=2) of

Rhythm Abnormalities

Adenosine induced a significant increase in the number of nodal and ventricular extrasystoles and bigeminisms in both groups in a dose-dependent manner; these reverted with DPCPX. The members of the control group suffered more bigeminisms (P < .05) (Figure 3).

TABLE 1. Effect of Adenosine on the Electrocardiographic Variables of Healthy and Chagasic Rat Hearts

<table>
<thead>
<tr>
<th>[Ado], (µmol)</th>
<th>PR, ms</th>
<th>QRS, ms</th>
<th>QT, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Chagasic</td>
<td>Control</td>
</tr>
<tr>
<td>0</td>
<td>53.78 (1.82)</td>
<td>57.3 (5.1)</td>
<td>15 (1.41)</td>
</tr>
<tr>
<td>10</td>
<td>55.78 (2.42)</td>
<td>61.3 (7.36)</td>
<td>15.89 (1.48)</td>
</tr>
<tr>
<td>33</td>
<td>52 (2.45)</td>
<td>57.8 (5.13)</td>
<td>16 (1.43)</td>
</tr>
<tr>
<td>100</td>
<td>55.67 (1.99)</td>
<td>60.44 (2.97)</td>
<td>17.11 (1.72)</td>
</tr>
<tr>
<td>333</td>
<td>55.44 (3.62)</td>
<td>59.44 (2.18)</td>
<td>15.89 (0.68)</td>
</tr>
<tr>
<td>1000</td>
<td>54.83 (3.15)</td>
<td>60.5 (3.38)</td>
<td>16.13 (1.08)</td>
</tr>
</tbody>
</table>

Ado indicates adenosine. *P < .05 with respect to Ado 0 µmol.

TABLE 2. Effect of DPCPX in the Presence of Adenosine on the Electrocardiographic Variables of Healthy and Chagasic Rat Hearts

<table>
<thead>
<tr>
<th>[DPCPX] (nmol)</th>
<th>PR, ms</th>
<th>QRS, ms</th>
<th>QT, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Chagasic</td>
<td>Control</td>
</tr>
<tr>
<td>0</td>
<td>54.14 (2.86)</td>
<td>56.17 (3.59)</td>
<td>17.33 (1.01)</td>
</tr>
<tr>
<td>100</td>
<td>57.38 (4.58)</td>
<td>58.5 (2.26)</td>
<td>18.44 (0.6)</td>
</tr>
<tr>
<td>333</td>
<td>55 (4.19)</td>
<td>57.33 (3.31)</td>
<td>18 (0.85)</td>
</tr>
<tr>
<td>1000</td>
<td>59.22 (2.28)</td>
<td>60.14 (2.4)</td>
<td>17.56 (1.59)</td>
</tr>
<tr>
<td>3333</td>
<td>61.67 (1.86)</td>
<td>58.71 (1.41)</td>
<td>16.89 (1.53)</td>
</tr>
</tbody>
</table>

DPCPX indicates 1,3-dipropyl-8-cyclopentylxanthine. *P < .05 by ANOVA for paired samples; however, the Bonferroni test detected no significant differences between the doses tested. *P < .05 with respect to Ado 0 µmol. 0 represents perfusion with 333 µmol adenosine in the absence of DPCPX.

Figure 2. Prolongation of the QT interval induced by early post-depolarizations, R on T phenomena, torsade de pointes and ventricular fibrillation. A: recordings obtained for chagasic hearts in the presence (black line) and absence (red line) of 100 µmol adenosine; note the prolongation of the QT interval and early depolarizations (arrow); the amplitude was normalized to facilitate the superimposition of the recordings. B: premature ventricular complexes arising out of the T wave (R on T phenomenon). C: torsade de pointes. D: ventricular fibrillation.
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...of the A1 and A2a receptors. It is known that the probability of VF appearing, facilitated by hypoxia and reoxygenation phenomena, is reduced with DPCPX, confirming that the A1 receptors are involved in VF. It is also known that the ability of adenosine to induce VF is blocked by the depletion of catecholamines in the heart, confirming that adenosine induces VF under hypoxia-reoxygenation conditions via a mechanism facilitated by the activation of the adrenergic system.

In CCC, abnormalities of the coronary microcirculation lead to cycles of hypoxia, ischemia and reoxygenation. This would condition the chagasic heart to the profibrillatory action of adenosine, which, in the present model, was favored by the sustained activation of the beta-adrenergic receptors. The medical importance of this work lies in its linking of the arrhythmias associated with the prolonged QT interval with the A1 adenosinergic system. This opens up the possibility of studies designed to investigate the therapeutic effect of A1 antagonists in these arrhythmias.

REFERENCES


Figure 3. Bigeminisms induced by A1 receptors. Beige represents the control, red the treatment. All recordings were obtained from the same chagasic rat. A: adenosine dose-response curve. B: dose response curve for DPCPX in the presence of 333 µmol adenosine; recordings are baseline (left), perfusion with adenosine (middle) and perfusion with DPCPX-adenosine (right); the vertical line represents 100 µV and the horizontal 0.5 s.

- P<.05 with respect to baseline.
- P<.05 between groups at the dose indicated.