Investigation of the protective effects of L-carnitine and L-arginine on cardiovascular changes induced by ACTH and dexamethasone in rabbits*

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Aim: To determine the protective effects of L-carnitine on cardiovascular changes that may occur in rabbits treated with adrenocorticotropic hormone (ACTH) and dexamethasone (DEX).

Materials and methods: Rabbits of equal weight were divided into 7 groups with 6 animals in each. Blood samples were collected from all groups on days 1, 7, and 14, and blood pressure values and ECG monitoring were recorded. Nitric oxide (NO), creatine kinase MB (CK-MB), and troponin I (TnI) levels were determined in blood samples. Heart rate, QT, and corrected QT (QTc) values were calculated from ECG records.

Results: The QT and QTc times were prolonged significantly (P < 0.001) in the ACTH-treated groups compared to the control group, and L-carnitine had no protective effect. Moreover, CK-MB (P < 0.05) and TnI (P < 0.001) levels were higher in the ACTH-treated groups than they were in the control group.

Conclusion: Application of ACTH results in prolongation of QT and QTc intervals and increases in CK-MB and TnI levels, which are indicators of heart muscle damage.

Key words: Nitric oxide, QT, CK-MB, troponin, ACTH, carnitine

1. Introduction
Acute and chronic stresses increase the risk of atherosclerosis and coronary artery diseases (1). Cortisol and similar hormones released from the adrenal cortex are known as natural glucocorticoids (GCs) (2). Natural and synthetic GCs are known to cause increases in blood pressure by decreasing mRNA stabilization of endothelial nitric oxide synthase (eNOS) and slowing down its gene transcription. Nitric oxide (NO) plays a major role in the regulation of blood pressure. An increase in blood pressure when treated with glucocorticoids is associated with a decrease in NO production (3,4).

Many factors, mainly elevated blood pressure, may result in myocardial disorders. Electrocardiography (ECG) and biochemical markers are employed to detect defects in the myocardium accurately and immediately. Troponin I and creatine kinase MB (CK-MB) are examples of these biochemical markers (5,6).

L-carnitine is used to treat patients with ischemic heart disease, congestive heart incapability, and atherosclerotic peripheral artery disease (7). Gomez-Ameros et al. (8) showed that with its antioxidant nature propionyl-L-carnitine protects the liver and heart in the case of oxidative stress associated hypertension.

This study was performed to investigate the protective effect of L-carnitine and L-arginine on cardiovascular changes in rabbits injected with ACTH and dexamethasone (DEX).

2. Materials and methods
2.1. Animals and experimental design
This study was conducted on 42 New Zealand rabbits 10–14 months old of both sexes and between 2.7 and 3.1 kg body weight. The rabbits were fed a special rabbit pellet diet ad libitum. The animals were kept in cages with the room temperature set to 21 °C and with 12 h light/12 h dark schedule. The experimental protocol was approved by the Laboratory Animal Care and Use Committee of Kafkas University.

The animals were divided into 7 groups with 6 rabbits in each. The control group received 0.5 mL of isotonic solution per rabbit via subcutaneous injection twice daily for 14
days. A 0.5-mL dose of ACTH (Synacthen Depot, 1 mg/mL, Ciba-Geigy, Novartis Pharma AG, Basel, Switzerland) was given per rabbit via subcutaneous injection twice daily for 14 days. A single dose of DEX (Calvasone, 2 mg/mL; 50 mL, Sanovel Pharma, Istanbul, Turkey) was given at a dose of 0.2 mL per rabbit via subcutaneous injection daily for 14 days. L-carnitine solution (Carnitine, Oral, 30%, 20 mL, Sigma-Tau, Rome, Italy) was given orally for 14 days. L-arginine (Cat no: 11010, Fluka, SIGMA GmBH, Germany), which was dissolved in isotonic solution, was applied orally for 14 days as a single dose.

The experimental design and the treatments were as follows:

- **Group 1 (CG); n = 6,** isotonic solution, 1 mL per rabbit per day (subcutaneously);
- **Group 2 (ACTH); n = 6,** ACTH, 1 mg per rabbit per day (subcutaneously);
- **Group 3 (ACTH-LC); n = 6,** ACTH, 1 mg per rabbit per day (subcutaneously) + L-carnitine, 200 mg/kg/day (orally);
- **Group 4 (ACTH-LA); n = 6,** ACTH, 1 mg per rabbit per day (subcutaneously) + L-arginine, 200 mg/kg/day (orally);
- **Group 5 (DEX); n = 6,** DEX, 400 µg per rabbit per day (subcutaneously);
- **Group 6 (DEX-LC); n = 6,** DEX, 400 µg per rabbit per day (subcutaneously) + L-carnitine, 200 mg/kg/day (orally);
- **Group 7 (DEX-LA); n = 6,** DEX, 400 µg per rabbit per day (subcutaneously) + L-arginine, 200 mg/kg/day (orally).

### 2.2. Electrocardiography recording

The electrocardiographic procedure was performed as reported by Uzun et al. (9). ECG records were taken for all rabbits before the experiment (baseline) and on days 1, 7, and 14 of the experiment by direct writing electrocardiograph (Poly-Spectrum 12 channel ECG-System, Poly-Spectru-8, Neurosoft, Ivanovo, Russia). ECG recordings were loaded onto a computer and analyzed manually. No sedatives or anesthetics were given to the animals before or during ECG recording. ECG recordings standardized at 1 mV = 20 mm, with chart speed of 50 mm/s with filter and Leads I, II, III, aVR, aVL, and aVF were obtained. The QT interval was corrected for heart rate (HR) with the formula $\text{QTcF} = \text{QT}/(\text{RR}^{1/3})$ as described by Fridericia et al. (10).

### 2.3. Measurements of blood pressure

For the purpose of blood pressure measurements, the sensitive part of the device was tied to the brachial artery, which is located above the articulatio cubiti, in the foreleg of the rabbit. The systolic blood pressure (SBP), mean blood pressure (MBP), and diastolic blood pressure (DBP) values were recorded by the oscillometric method (Memoprint S+B, medVET GmBH, Germany) on days 1, 7, and 14 (11).

### 2.4. Collection of blood samples

Blood samples were collected from the V. auricularis of the animals in all groups 2 h after the injections on days 1, 7, and 14 of the experiment. Plasmas were separated by centrifugation at 3000 rpm for 10 min. Plasma samples were stored at −20 °C until the analysis following deproteinization.

### 2.5. Analysis of NO

Plasma NO levels were measured according to Miranda et al. (12). After the plasma samples were deproteinized with 10% zinc sulfate, the samples were centrifuged at 1400 rpm for 10 min. Then total NO concentrations (via NO metabolites: nitrate and nitrite) were determined with the acidic Griess reaction by colorimetric method.

### 2.6. Analysis of CK-MB and troponin I

CK-MB analyses were performed using spectrophotometric measurements (Cat. no. TR90231, IBL, Turkey). Tn I levels were determined by ELISA kit (Cat. no. EIA-2952, IBL, Turkey).

### 2.7. Statistical analysis of data

Data were analyzed with MINITAB statistical software (Minitab Inc., Pennsylvania, USA). Differences between the groups at the same sampling time and differences between the sampling times within the groups for QT, QTc, RR, SBP, MBP, DBP, HR, NO, CK-MB, and TnI values were determined with one-way ANOVA. Pearson’s correlation was used to determine the relationships between the investigated parameters. All of the data are expressed as means ± SEMs. The level of significance was set at $P < 0.05$.

### 3. Results

In NO levels, the only significant difference was observed on day 1 in the DEX-LC group. NO levels on each sampling day with statistical significance are indicated in Table 1 ($P < 0.05$).

There was no significant difference between the groups in terms of CK-MB activity on day 1 of the experiment. CK-MB values were higher in all ACTH applied groups. The highest value of CK-MB was $581 \pm 248$ U/L on day 7 when ACTH was applied and $289 \pm 58$ U/L on day 14 when ACTH-LA was applied. It was also found that the difference between ACTH and DEX-LA on day 7 and the difference between ACTH-LA and DEX-LA on day 14 were significant ($P < 0.05$; Table 1).

No significant difference was observed between days 1 and 7 in TnI levels between the groups. Nevertheless, an increase in the level of TnI was detected in the ACTH applied group in comparison to the other groups. The level of TnI on day 14 in the ACTH-LC group was significantly different compared to that in the CG, DEX, DEX-LC, and DEX-LA groups ($P < 0.001$; Table 1).
HR was higher in the ACTH applied group in comparison to the control and DEX groups and the difference was significant on some sampling days. The mean values of pulse in all groups and the level of significance are presented in Table 2.

In comparison to the control group, QT and QTc times on days 1, 7, and 14 were significantly prolonged (P < 0.001) in all 3 ACTH applied groups.

The SBP, DBP, and MBP values and the differences between the groups on days 1, 7, and 14 are shown in Table 3. A lower systolic blood pressure level was observed in the ACTH-LA applied group compared to the other groups, whereas in the DEX applied groups it was highest on day 14. Moreover, the differences between the ACTH-LA (92 ± 4 mmHg), DEX (117 ± 7 mmHg), and DEX-LC (117 ± 5 mmHg) groups in terms of SBP were statistically significant (P < 0.05).

### Table 1. The NO, CK-MB, and troponin I levels in the control and treatment groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day</th>
<th>CG (n = 6)</th>
<th>ACTH (n = 6)</th>
<th>ACTH-LC (n = 6)</th>
<th>ACTH-LA (n = 6)</th>
<th>DEX (n = 6)</th>
<th>DEX-LC (n = 6)</th>
<th>DEX-LA (n = 6)</th>
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<td>NO*</td>
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<td>37 ± 2a</td>
<td>38 ± 4ab</td>
<td>46 ± 4ab</td>
<td>46 ± 3ab</td>
<td>55 ± 4a</td>
<td>42 ± 4ab</td>
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<tr>
<td></td>
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<td>14</td>
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<td>39 ± 1</td>
<td>47 ± 3</td>
<td>42 ± 5</td>
<td>47 ± 3</td>
<td>43 ± 2</td>
<td>43 ± 3</td>
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<tr>
<td>CK-MB*</td>
<td>1</td>
<td>113 ± 28</td>
<td>215 ± 56</td>
<td>250 ± 62</td>
<td>325 ± 123</td>
<td>147 ± 48</td>
<td>65 ± 10</td>
<td>149 ± 47</td>
</tr>
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<td></td>
<td>7</td>
<td>106 ± 28ab</td>
<td>581 ± 248a</td>
<td>313 ± 97ab</td>
<td>412 ± 116ab</td>
<td>152 ± 40ab</td>
<td>105 ± 45ab</td>
<td>76 ± 20b</td>
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<td>14</td>
<td>145 ± 30ab</td>
<td>159 ± 31ab</td>
<td>190 ± 32ab</td>
<td>289 ± 58ab</td>
<td>148 ± 31ab</td>
<td>152 ± 76ab</td>
<td>34 ± 40b</td>
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<td>Tn I**</td>
<td>1</td>
<td>0.036 ± 0.02</td>
<td>0.178 ± 0.07</td>
<td>0.125 ± 0.06</td>
<td>0.076 ± 0.02</td>
<td>0.036 ± 0.02</td>
<td>0.035 ± 0.02</td>
<td>0.045 ± 0.02</td>
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<td>0.021 ± 0.01</td>
<td>0.414 ± 0.20</td>
<td>0.242 ± 0.06</td>
<td>0.279 ± 0.10</td>
<td>0.376 ± 0.31</td>
<td>0.050 ± 0.03</td>
<td>0.134 ± 0.07</td>
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<tr>
<td></td>
<td>14</td>
<td>0.017 ± 0.02</td>
<td>0.132 ± 0.03abc</td>
<td>0.232 ± 0.07b</td>
<td>0.151 ± 0.07abc</td>
<td>0.017 ± 0.02</td>
<td>0.013 ± 0.01ac</td>
<td>0.028 ± 0.02ac</td>
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</tbody>
</table>

*: P < 0.05, **: P < 0.001. The values within the same row with different superscripts differ significantly.

### Table 2. The heart rate, QT, and QTc values in the control and treatment groups.

<table>
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<tr>
<th>Parameters</th>
<th>Day</th>
<th>CG (n = 6)</th>
<th>ACTH (n = 6)</th>
<th>ACTH-LC (n = 6)</th>
<th>ACTH-LA (n = 6)</th>
<th>DEX (n = 6)</th>
<th>DEX-LC (n = 6)</th>
<th>DEX-LA (n = 6)</th>
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<td>HR</td>
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<td>238 ± 6ad</td>
<td>257 ± 9b</td>
<td>248 ± 12ab</td>
<td>243 ± 12bd</td>
<td>209 ± 9c</td>
<td>230 ± 9d</td>
<td>240 ± 13ad</td>
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<tr>
<td></td>
<td>7</td>
<td>251 ± 9ab</td>
<td>246 ± 6ad</td>
<td>264 ± 7bc</td>
<td>272 ± 6c</td>
<td>231 ± 13d</td>
<td>251 ± 10b</td>
<td>245 ± 13ad</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>233 ± 7a</td>
<td>249 ± 12abc</td>
<td>265 ± 15b</td>
<td>253 ± 11bc</td>
<td>243 ± 7c</td>
<td>234 ± 15c</td>
<td>244 ± 13ac</td>
</tr>
<tr>
<td>QT</td>
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<td>133 ± 2a</td>
<td>144 ± 4a</td>
<td>154 ± 9a</td>
<td>153 ± 6c</td>
<td>138 ± 5bc</td>
<td>136 ± 2b</td>
<td>135 ± 3c</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>14</td>
<td>139 ± 1a</td>
<td>155 ± 5b</td>
<td>142 ± 7ad</td>
<td>149 ± 4bc</td>
<td>142 ± 3d</td>
<td>147 ± 4d</td>
<td>143 ± 3ac</td>
</tr>
<tr>
<td>QTc</td>
<td>1</td>
<td>210 ± 4a</td>
<td>232 ± 5b</td>
<td>246 ± 11c</td>
<td>243 ± 6bc</td>
<td>209 ± 8c</td>
<td>213 ± 1c</td>
<td>214 ± 3c</td>
</tr>
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<td></td>
<td>7</td>
<td>213 ± 4ace</td>
<td>234 ± 3c</td>
<td>245 ± 4ad</td>
<td>248 ± 5d</td>
<td>227 ± 4c</td>
<td>228 ± 7c</td>
<td>220 ± 4bc</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>218 ± 2a</td>
<td>248 ± 5bd</td>
<td>231 ± 10a</td>
<td>240 ± 7ad</td>
<td>226 ± 4ac</td>
<td>230 ± 4c</td>
<td>227 ± 2c</td>
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</tbody>
</table>

The values within the same row with different superscripts differ significantly (P < 0.001).
the prolongations in these groups were less than those in the ACTH treated groups. Increases in TnI and CK-MB levels, which are indicators of cardiac damage, in the groups that showed prolonged QT and QTc times may suggest cardiac damage. Considering the protective effect of L-carnitine on day 14 on the damage induced by ACTH and DEX, although the QT and QTc values in the ACTH-LC group were higher than those in the CG, the existence of lower values compared to the ACTH and ACTH-LA groups can be considered as showing that L-carnitine has slightly shortened the prolongation of QT and QTc times.

NO, a strong vasodilator that is effective on the continuation of arterial tone in pulmonary, coronary, and systemic circulation, is an agent affecting the maintenance of vascular tone in vessels in humans and other species (16). Although the impact of endothelium-derived NO on vessels is well known, its autocrine and paracrine effects on the heart muscle have been recently highlighted. Low doses of NO and NO donors, which have different effects on the heart, lead to a positive inotropic effect, which is considered to increase basal cardiac function. On the other hand, when given in high doses, they increase myocyte relaxation or diastolic function (17). In other studies, it was claimed that NO influences the autonomic nervous control of cardiac pulse directly (18), and it facilitates the ability of the sinoatrial node to create stimulation (19).

In the present study, statistically significant differences were observed between the groups in terms of NO levels on day 1 while no differences were determined on days 7 and 14. In the DEX-LC group, determination of an increase in NO levels on day 1 suggests that L-carnitine, like L-arginine, leads to an increase in NO production (20). In addition, no significant correlation between NO levels and SBP, DBP, MBP, HR, QT, QTc, CK-MB, and TnI levels was determined in our investigation. Although there was no correlation between NO levels and blood pressure, the lower NO levels in the ACTH group compared to the CG and other groups, and, considering the blood pressure values on days 7 and 14, the existence of higher blood pressure in the ACTH group than in the ACTH-LC and ACTH-LA are consistent with the results of studies indicating that plasma nitrate/nitrite level is reduced while blood pressure is increased by ACTH treatment (21,22).

Some researchers (21,23) have reported that increases in blood pressure due to ACTH through its stimulatory effects on cortisol and corticosterone secretion are eliminated by L-arginine application. It has also been reported that L-arginine decreases blood pressure in hypertension and reduces the proliferation of vascular smooth muscle cells by increasing NO production (20). In a study conducted by Gomez-Amores et al. (8), it was indicated that propionyl-L-carnitine protects the rat heart and liver in the case of oxidative stress-related hypertension because of its antioxidant properties.

In this study, although increases were determined in SBP, DBP, and MBP values following elevated ACTH levels and after the application of DEX, the protective effect of L-arginine was observed on days 7 and 14. This situation suggests that the efficacy of DEX for increasing the blood pressure is higher than that of ACTH. Furthermore, when the L-carnitine was given to the ACTH and DEX treated groups, a slight but not significant reduction was observed in blood pressure values on days 7 and 14. The reduced BP suggests that L-carnitine may also have a protective effect against the elevated blood pressure resulting from ACTH and DEX application. However, it can be speculated that this protective effect is not as effective as that of L-arginine, because when the groups are compared in terms of SBP on day 7 the SBP value was 113 ± 12 mmHg in the group treated with ACTH, whereas in the ACTH-LC group this

Table 3. The SBP, DBP, and MBP values in the control and treatment groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Day</th>
<th>CG (n = 6)</th>
<th>ACTH (n = 6)</th>
<th>ACTH-LC (n = 6)</th>
<th>ACTH-LA (n = 6)</th>
<th>DEX (n = 6)</th>
<th>DEX-LC (n = 6)</th>
<th>DEX-LA (n = 6)</th>
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<tr>
<td>SBP</td>
<td>1</td>
<td>105 ± 5</td>
<td>99 ± 4</td>
<td>103 ± 4</td>
<td>109 ± 6</td>
<td>111 ± 9</td>
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<td>7</td>
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<td>113 ± 12</td>
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<td>119 ± 5</td>
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<td></td>
<td>14</td>
<td>106 ± 6abc</td>
<td>105 ± 8abc</td>
<td>106 ± 3abc</td>
<td>92 ± 4a</td>
<td>117 ± 7b</td>
<td>117 ± 5bc</td>
<td>108 ± 4abc</td>
</tr>
<tr>
<td>DBP</td>
<td>1</td>
<td>68 ± 4abc</td>
<td>56 ± 3b</td>
<td>59 ± 4abc</td>
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<td>76 ± 2</td>
<td>66 ± 4</td>
<td>86 ± 6</td>
<td>85 ± 4</td>
<td>76 ± 4</td>
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</table>

The values within the same row with different superscripts differ significantly (P < 0.05).
value was 99 ± 6 mmHg and in the ACTH-LA group it fell to 91 ± 2 mmHg. A similar situation was observed in the groups treated with DEX; the values of SBP on day 7 in the groups treated with DEX, DEX-LC, and DEX-LA were 119 ± 7 mmHg, 124 ± 10 mmHg, and 119 ± 5 mmHg, respectively. In general, a similar trend was observed for DBP and mean BP values, suggesting that the protective effects of L-carnitine and L-arginine emerge on days 7 and 14. In addition, the determination of different BP values in the ACTH and DEX treated groups as well as the lowering effect of L-arginine not being to the same extent as L-carnitine may show that both substances have different efficacies and mode of actions for diminishing blood pressure.

Troponin, an important marker of cardiac damage, regulates calcium-mediated actin and myosin interaction (24). Troponin is in 3 isoforms: TnI, TnT, and TnC. Troponin I and T are specific markers of heart muscle damage. TnT increases with kidney and muscle tissue injuries. TnI is regarded as one of the most specific indicators of acute myocardial infarction (25). Another marker of cardiac damage is creatine kinase (CK). This enzyme has 3 isoforms (26). One of them is CK-MB, which is specific for heart muscle. The CK level, especially CK-MB level, increases significantly due to myocardial damage, and so is regarded as an important indicator of heart muscle damage (27,28). Many factors, in particular increase in blood pressure, may cause damage to the heart muscle.

In the present study, statistically significant increases were determined on days 7 and 14. CK-MB and TnI levels are important markers of cardiac damage (5,6). The effect of ACTH on CK-MB and TnI is more obvious than that of DEX. In the CG, CK-MB level was 106 ± 28 U/L, whereas this value reached 581 ± 248 U/L in the ACTH treated group and in the DEX treated group it was 152 ± 40 U/L on day 7. On day 14, CK-MB levels in the CG and ACTH and DEX groups were 145 ± 30 U/L, 159 ± 31 U/L, and 148 ± 31 U/L, respectively. L-carnitine and L-arginine were used for prophylactic purposes against ACTH and DEX; they slightly but not significantly decreased CK-MB activity. CK-MB enzyme is an indicator of cardiac damage and its level is increased by damage to heart muscle cells. Therefore, it is accepted as an indicator of myocardial damage (27,28). The increase in CK-MB level in the group treated with ACTH suggests that ACTH leads to damage to the heart muscle cells.

The results of this study showed that ACTH applications can cause damage to heart muscle cells, resulting in elevation of cardiac enzymes, but L-carnitine and L-arginine have no protective effects. However, DEX, a synthetic glucocorticoid, does not cause severe damage as ACTH does, and the negative impact of ACTH on the heart muscle is the result of increased cortisol concentration. In addition, ACTH and DEX applications may lead to cardiac arrhythmias due to prolonged QT and QTc intervals, but there is no correlation between the prolongation of QT and QTc times and NO and blood pressure.

References


