



## **Original Article**

### **The Ameliorative Effect of Vitamin E on Electrocardiogram of Rabbits Exposed to Cadmium Chloride**

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## **Abstract**

This study was designed to study the effect of cadmium as an oxidant agent on electrocardiogram (ECG) component and the possible preventive role of vitamin E on deleterious effects of cadmium in adult male rabbits. Twenty adult male rabbits were divided randomly into 4 equal groups (5 animals /group) and treated daily for 84 days. The first group were received ordinary tap water and serve as control (C); the second group (T1) received *ad libitum* supply of drinking water containing (50ppb) cadmium chloride; the third group T2 received (50ppb) of cadmium chloride in drinking water, in addition to intubation of vitamin E (40mg/Kg B.W.) orally, while the fourth group (T3) were intubated daily with 40mg/Kg B.W of vitamin E. Fasting blood samples were collected at 0, 21, 42, 63 and 84 days of the experiment to determine serum calcium concentration . The ECG was also recorded in all groups at the same interval of the experiment. The results revealed that administration of 50 ppb CdCl<sub>2</sub> in drinking water (T1 group) for 84 days caused a significant decrease ( $p < 0.05$ ) in serum calcium concentration as compared to control. On other hand, the animals treated with vitamin E (T2 and T3) showed, no significant ( $p > 0.05$ ) differences in this parameter as compared to control and other groups. Analysis of ECG in Cadmium treated group (T1) showed significant ( $p < 0.05$ ) differences represented by significant prolongation of P wave, T wave, QRS complex and P-Q as well as Q-T interval, with a significant ( $p < 0.05$ ) decreased of heart rate as compared to the control and vitamin E treated groups (T2 and T3) which clarified non-significant ( $p > 0.05$ ) differences in ECG waves analysis. In conclusion, Cadmium effect on electrical conduction of heart was represented by abnormality in some of ECG component as well as the protective role of vitamin E as antioxidant in the cardiovascular system was also confirmed.

**Key Words:** Cadmium chloride, ECG, Calcium, Vitamin E.

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## Introduction

The heavy metal cadmium (Cd) a pollutant associated with several modern industrial processes such as pigments, stabilizers, alloys ,electronic compounds, and especially in rechargeable nickel-cadmium batteries ( Jarup ,2003;Cannino et al., 2009) . Human intoxication results mainly from cigarette smoking due to high concentrations of Cd in cigarettes (Tsutsumi et al., 2009). There has been increasing interest in the potential adverse cardiovascular effects of environmental exposures, including heavy metals (Weinhold, 2004; Bhatnagar, 2006; Houston, 2007). Cadmium has been reported to have cumulative effects on mortality, cardiovascular, neurologic, renal, and developmental diseases (ICEIT, 2009). Increased cadmium body burden is associated with lower aortic pulse wave velocity, lower pulse pressure throughout the arterial system, and higher femoral distensibility (Schutte *et al*, 2008). A long-term-Cd<sup>+2</sup> exposure increased stroke volume (SV) and cardiac output (CO) (Ozturk *et al*,2009). A recent large USA study found an association between U-Cd and myocardial infarction (Zaslavina *et al.*, 2007; Everett and Frithsen, 2008).

Reports have shown that antioxidants like vitamin C and Vitamin E have shown protection against cadmium induced toxicity in different animal models (Beytut et al., 2003; Ognjanovic et al., 2003).  $\alpha$ -tocopherol can reduce Cd-induced oxidative stress and improve the glutathione level together with other biochemical parameters (Nemmiche et al .,2007).This study was designed to study the effect of chronic exposure to cadmium chloride on electrocardiograph of adult male rabbits and the protective role of vitamin E.

## Materials and Methods

Twenty male rabbits were randomly divided into four equal groups (each group consist of five rabbits) and were treated for 84 days as follow: Group I (control), Group II: rabbits of this group were received *ad libitum* supply of drinking water containing (50ppb) cadmium chloride, Group III: rabbits of this group were received *ad libitum* supply of drinking water containing (50ppb) cadmium chloride and 40 mg/kg B.W. of vitamin E ((RRR- $\alpha$ -tocopherol) orally. ECGs were recorded by a direct writing electrocardiograph (Cardisuny type A; Fucuda M.E Kogyo Co., LTD Japan). This study was approved by research committee/ Department of Physiology and Pharmacology / College of Veterinary Medicine / Baghdad University, Iraq. All ECGs were standardized at 1 mV = 10 mm, with a chart speed of 50 mm/sec. Leads I, II, III, aVR, aVL and aVF were recorded at 0,21,42,63 and 84 and calculation was done according to Reisner and his coworkers (2006) and Serum calcium concentration was determined as described by Cali et al., (1972). Statistical analysis of data was performed on the basis of two- way analysis of variance (ANOVA) depending on the experimental design at each time .Specific group differences were determined using least significant differences (LSD) test (Steel and Terrie, 1980).

## Results

### Serum calcium concentration (mg/dl)

A significant ( $P < 0.05$ ) decrease in serum calcium concentration was recorded after different days of experiment (21, 42, 63 and 84 days) in Cd exposure group (T1) as compared to the control and other treated groups (T2 and T3). No significant ( $P > 0.05$ ) differences was observed in the mean value of this parameter in both vitamin E treated groups (T2 and T3) after the same duration of treatment (84 days) as compared to control group, as well as when they compared with each other (table.1) .

Days	Groups			
	(C) Control group.	(T1) 50 ppb of CdCl <sub>2</sub> in drinking water	(T2) 50ppb of CdCl <sub>2</sub> + 40mg Vit.E.	(T3) 40mg Vit.E.
Zero	12.20±0.30 A a	12.70±0.10 A a	12.40±0.20 A a	12.20±0.22 A a
21	12.50±0.40 A a	10.90±0.10 B b	12.50±0.50 A a	12.10±0.20 A a
42	12.40±0.20 A a	9.80±0.10 B c	12.50±0.40 A a	12.22±0.22 A a
63	12.10±0.20 A a	8.80±0.10 B d	12.10±0.20 A a	11.80±0.20 A a
84	12.10±0.10 A a	7.50±0.10 B e	12.0±0.20 A a	12.10±0.40 A a

Table.1: Effect of cadmium chloride and vitamin E on Ca<sup>++</sup> concentration (mg/dl) in serum of rabbits. Values are expressed as mean ± SE, n = 5 each group , Capital letters denote differences between groups,  $P < 0.05$  vs. control. , Small letters denote differences within group,  $P < 0.05$  vs. control.

### Electrocardiograph

#### P -wave interval and amplitude

After 42, 63 and 84 days of treatment with cadmium chloride (T1 group) a significant ( $P < 0.05$ ) differences in p- wave interval (p/sec) was observed comparing to control and treated groups (T2 and T3), while p- wave amplitude (p/mv) did not show significant ( $P > 0.05$ ) differences in T1 group as compared to control, T2 and T3 groups in the same duration of experiment (after 84 days). A significant ( $P < 0.05$ ) prolongation was observed in p/sec at the days at 84 of the treatment in rabbits received 50 ppb of CdCl<sub>2</sub>(T1) as compared to the pretreatment period (table-2 and figure-2).

Groups	C		T1		T2		T3	
Days	P/sec.	P/mv	P/sec.	P/mv	P/sec.	P/mv	P/sec.	P/mv
Zero	0.042± 0.002 A a	0.10± 0.01 A a	0.046± 0.002 A a	0.08± 0.01 A a	0.040± 0.003 A a	0.10± 0.02 A a	0.042± 0.002 A a	0.09± 0.01 A a
21	0.044± 0.002 A a	0.08± 0.01 A a	0.052± 0.004 A ab	0.08± 0.01 A a	0.046± 0.004 A a	0.09± 0.01 A a	0.044± 0.002 A a	0.08± 0.01 A a
42	0.044± 0.002 A a	0.08± 0.01 A a	0.054±0.0 04 B ab	0.09±0.01 A a	0.046±0.004 A B a	0.09±0.01 A a	0.044± 0.002 A a	0.09± 0.01 A a
63	0.042± 0.002 A a	0.08± 0.01 A a	0.056± 0.002 B b	0.07± 0.01 A a	0.040± 0.002 A a	0.09± 0.01 A a	0.044± 0.002 A a	0.08± 0.01 A a
84	0.042± 0.002 A a	0.08± 0.01 A a	0.066± 0.004 B c	0.07± 0.01 A a	0.044± 0.002 A a	0.08± 0.01 A a	0.044± 0.002 A a	0.09± 0.01 A a

Table .2: Effect of cadmium chloride and vitamin E on P- wave interval (second) and p-amplitude (mv) in ECG of rabbits. Values are expressed as mean  $\pm$  SE, n = 5 each group , Capital letters denote differences between groups, P<0.05 vs. control. , Small letters denote differences within group, P< 0.05 vs. control.

#### T- Wave interval (second) and T amplitude (mille volt):

Results in table (3) showed a significant (P<0.05) prolongation in T- wave interval (T/sec) at the days 21, 42, 63 and 84 of the treatment in rabbits received 50 ppb of CdCl<sub>2</sub> (T1) (figures 2,3) as compared with the control group and treated groups (T2 and T3). Also there were no significant differences (P>0.05) in the mean values of T/sec for T2 and T3 groups after 84 days of treatment when they compared to the control group as well as to each other. A significant (P<0.05) differences in T/sec were observed in (T1) treated group at the end of the experiment comparing to the pretreated period.

#### P-Q interval (second) and Q-T interval (second)

Values of P-Q and Q-T interval for the treated groups T1, T2, T3 and the control were depicted in table (4). While there were no significant (P>0.05) differences in the mean values between experimental groups during pretreated period, a significant increase (P<0.05) in the mean value of these parameters of T1 group was observed (figures 2, 3) after 21,42,63 and 84 days of the experiment comparing with the control and treated groups (T2 and T3). The results also clarified that treatment of male rabbits with vitamin E (T2 and T3 groups) did not cause significant (P>0.05) differences after 84 days of experiment as compared to the control. Moreover, no significant (P>0.05) differences between T2 group and T3 group were observed at

the end of experiment. A significant ( $P<0.05$ ) increase was manifested within the time in the mean values of P-Q/sec and Q-T/sec after treatment of adult male rabbits with cadmium chloride in drinking water (T1) as compared to pretreated period.

Groups	C		T1		T2		T3	
Days	T/sec.	T/mv	T/sec.	T/mv	T/sec.	T/mv	T/sec.	T/mv
Zero	0.056± 0.002 A a	0.16± 0.010 A a	0.056± 0.005 A a	0.16± 0.010 A a	0.055± 0.003 A a	0.17± 0.01 A a	0.060± 0.003 A a	0.16± 0.010 A a
21	0.056± 0.002 A a	0.15± 0.015 A a	0.080± 0.003 B b	0.18± 0.010 A a	0.060± 0.003 A a	0.18± 0.01 A a	0.060± 0.001 A a	0.16± 0.020 A a
42	0.056± 0.002 A a	0.15± 0.020 A a	0.082± 0.005 B b	0.17± 0.012 A a	0.058± 0.004 A a	0.18± 0.03 A a	0.060± 0.003 A a	0.15± 0.015 A a
63	0.058± 0.002 A a	0.15± 0.015 A a	0.090± 0.004 B c	0.16± 0.010 A a	0.058± 0.002 A a	0.16± 0.01 A a	0.056± 0.002 A a	0.17± 0.015 A a
84	0.058± 0.002 A a	0.16± 0.010 A a	0.098± 0.002 B d	0.18± 0.010 A a	0.060± 0.003 A a	0.16± 0.01 A a	0.060± 0.003 A a	0.16± 0.010 A a

Table -3: Effect of cadmium chloride and vitamin E on T wave interval (second) and T amplitude (mv) in ECG of rabbits. Values are expressed as mean  $\pm$  SE, n = 5 each group , Capital letters denote differences between groups,  $P<0.05$  vs. control. , Small letters denote differences within group,  $P<0.05$  vs. control.

Groups	C		T1		T2		T3	
Days	P-Q/ sec.	Q-T/ sec.	P-Q/ sec.	Q-T/ sec.	P-Q/ sec.	Q-T/ sec.	P-Q/ sec.	Q-T/ sec.
Zero	0.058± 0.002 A a	0.128± 0.003 A a	0.058± 0.005 A a	0.124± 0.004 A a	0.060± 0.002 A a	0.130± 0.004 A a	0.060± 0.003 A a	0.130± 0.004 A a
21	0.058± 0.004 A a	0.126± 0.004 A a	0.072± 0.004 B b	0.148± 0.004 B b	0.062± 0.002 A a	0.128± 0.004 A a	0.058± 0.004 A a	0.126± 0.004 A a
42	0.060± 0.003 A a	0.126± 0.004 A a	0.074± 0.004 B b	0.154± 0.004 B bc	0.060± 0.003 A a	0.124± 0.004 A a	0.060± 0.003 A a	0.125± 0.005 A a
63	0.060± 0.003 A a	0.124± 0.004 A a	0.076± 0.002 B b	0.164± 0.004 B cd	0.058± 0.002 A a	0.128± 0.005 A a	0.060± 0.003 A a	0.123± 0.004 A a
84	0.060± 0.003 A a	0.126± 0.004 A a	0.078± 0.022 B b	0.168± 0.004 B d	0.058± 0.002 A a	0.126± 0.004 A a	0.060± 0.004 A a	0.124± 0.004 A a

Table.4: Effect of cadmium chloride and vitamin E on P-Q interval (second) and Q-T interval (second) in ECG of rabbits. Values are expressed as mean  $\pm$  SE, n = 5 each group , Capital letters denote differences between groups,  $P < 0.05$  vs. control. , Small letters denote differences within group,  $P < 0.05$  vs. control.

### QRS complex interval (second)

The results showed no significant differences ( $P > 0.05$ ) in the mean value of QRS/sec of control and treatment groups at 0 ,21 ,42, and 63 days of the experiment when compared to each other(table-5) . On the other hand, a significant ( $P < 0.05$ ) increase was recorded in mean value of this wave in cadmium treated group (T1) at 84 day (figure-3) as compared to the control and vitamin E treated groups (T2 and T3). The results have clarified that the mean value of QRS/sec in T2 group and T3 group did not show significant differences ( $P > 0.05$ ) comparing to the control group as well as to each other in the same duration of the experiment. Within the time T1 group showed a significant ( $P < 0.05$ ) prolongation in QRS wave interval at day 84 of experiment as compared to the pretreatment period.

### Heart rate :

A significant decrease ( $P < 0.05$ ) in mean value of heart rate was detected at days 42 ,63 and 84 in Cd exposed group (T1) comparing to the control ,T2 and T3 groups . Depending on the statistical results, each of vitamin E treated groups (T2 and T3) did not show significant ( $P > 0.05$ ) differences in the mean value of heart rate when they compared to control group as well as to each other(table-6)

Groups	( C ) Control group.	T1 50 ppb of CdCl <sub>2</sub> in drinking water	T2 50ppb of CdCl <sub>2</sub> + 40mg Vit. E.	T3 40mg Vit.E.
Days				
Zero	0.034 $\pm$ 0.004 A a	0.032 $\pm$ 0.033 A a	0.030 $\pm$ 0.003 A a	0.032 $\pm$ 0.002 A a
21	0.032 $\pm$ 0.002 A a	0.034 $\pm$ 0.002 A a	0.032 $\pm$ 0.003 A a	0.034 $\pm$ 0.002 A a
42	0.034 $\pm$ 0.002 A a	0.038 $\pm$ 0.002 A ab	0.034 $\pm$ 0.002 A a	0.034 $\pm$ 0.002 A a
63	0.034 $\pm$ 0.002 A a	0.038 $\pm$ 0.003 A ab	0.034 $\pm$ 0.002 A a	0.034 $\pm$ 0.002 A a
84	0.034 $\pm$ 0.002 A a	0.044 $\pm$ 0.002 B b	0.032 $\pm$ 0.002 A a	0.034 $\pm$ 0.002 A a

Table (5): Effect of cadmium chloride and vitamin E on QRS complex interval (second) ECG of rabbits. Values are expressed as mean  $\pm$  SE, n = 5 each group , Capital letters denote differences between groups,  $P < 0.05$  vs. control. , Small letters denote differences within group,  $P < 0.05$  vs. control.

Groups	C	T1	T2	T3
Days	Control group.	50 ppb of CdCl <sub>2</sub> in drinking water	50ppb of CdCl <sub>2</sub> + 40mg Vit. E.	40mg Vit.E.
Zero	288.8±6.90 A a	288.8±6.90 A a	288.8±6.90 A a	284.4±10.2 A a
21	294.4±5.61 A a	290.4±8.90 A a	294.4±5.60 A a	294.4±5.60 A a
42	291.4±5.70 A a	270.8±8.40 B b	288.8±6.90 A a	288.8±6.90 A a
63	288.4±5.30 A a	252.0±2.010 B c	288.8±6.90 A a	288.8±6.90 A a
84	291.4±5.70 A a	242.8±7.90 B c	288.8±6.90 A a	288.8±6.90 A a

Table.6: Effect of cadmium chloride and vitamin E on Heart rate (beat/mint) of rabbits. Values are expressed as mean  $\pm$  SE, n = 5 each group , Capital letters denote differences between groups, P<0.05 vs. control. , Small letters denote differences within group, P< 0.05 vs. control.

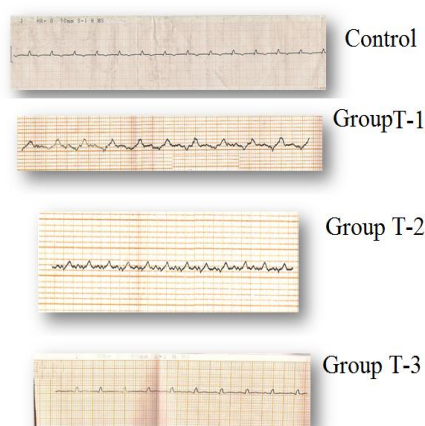


Figure. 1: Lead I of electrocardiograph for male rabbits in control, T1, T2, and T3 groups at the end of experiment.

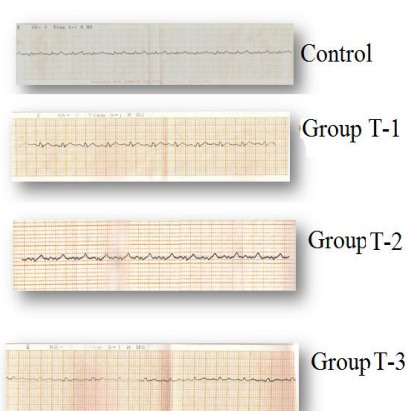


Figure. 2: Lead II of electrocardiograph for male rabbits in control, T1, T2, and T3 groups at the end of experiment.

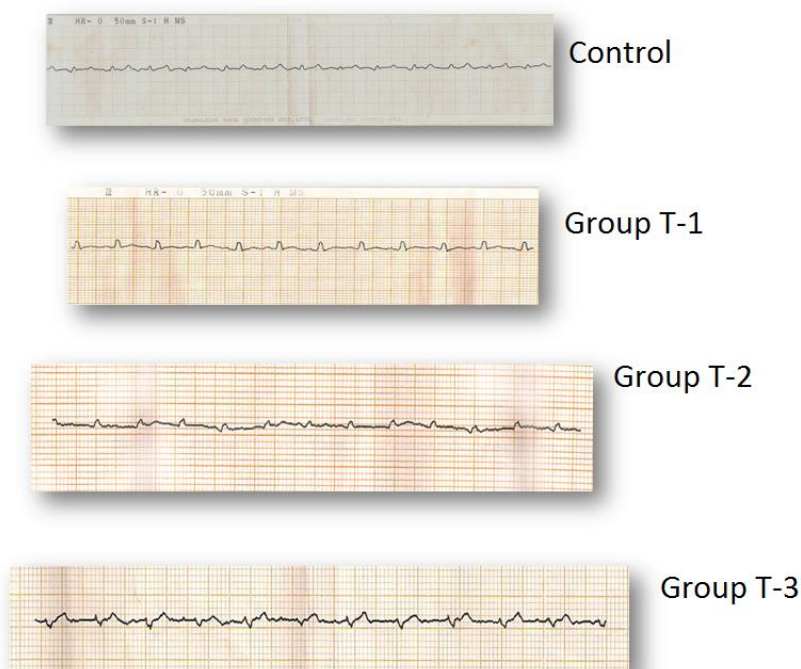


Figure. 3: Lead III of electrocardiograph for male rabbits in control, T1, T2, and T3 groups at the end of experiment.

## DISCUSSION

A significant decrease in Calcium ions concentration after cadmium treatment observed in the present study could be attributed to the similarity between hydrated radius of  $\text{Cd}^{2+}$  and  $\text{Ca}^{2+}$ , which lead to inhibition of receptor and voltage operated calcium channels as well as all types of  $\text{Ca-ATPases}$  pumps (Zhang et al., 1990; McNulty and Taylor, 1999; Saderholm et al., 2000 and Baldisserotto et al., 2004). Cadmium can interfere for uptake with essential metal ions including calcium (Ca), zinc (Zn) and copper (Cu), it is affect  $\text{Ca}^{2+}$  signaling in hepatic cells (Blazka and Shaikh 1992, Dundjerski *et al.* 2000, Baker *et al.* 2003). Biagioli *et al.*, (2008), observed that cadmium decreased agonist-evoked endoplasmic reticulum (ER)  $\text{Ca}^{2+}$  signals and caused a 40% inhibition of sarcoplasmic-ER calcium ATPases activity leading to depression in serum calcium concentration. The enhancement effect of vitamin E on the elevation of calcium concentration might be attribute either to a direct increase in the entry of  $\text{Ca}^{2+}$  through voltage - dependent  $\text{Ca}^{2+}$  channels or secondary effects resulting from, for example, modulation of  $\text{K}^{+}$  channels with the consequent alteration in plasma membrane potential (Yang and Wang , 2008).



The results of the present study showed significant prolongation of P wave, T wave, QRS complex and P-Q as well as Q-T interval, with a significant ( $p<0.05$ ) decreased of heart rate as compared to the control and vitamin E treated groups (T2 and T3).

P-wave analysis has long been used to study the atrial electrical activity (depolarization and repolarization) in the heart (Birkbeck *et al.*, 2006, Dilaveris and Stefanadis, 2009; Davey, 2010). Prolonged P-wave duration is a useful predictor of atrial fibrillation (AF) development (Ciaroni *et al.*, 2000, De *et al.*, 2007, Dilaveris and Stefanadis, 2009). Atrial repolarization starts during the PQ (PR) segment and continues into the QRS complex (Ihara *et al.*, 2006). A long PR interval reflects slow conduction through the atrioventricular (AV) node and bundle of His, and may indicate a disease of the conducting tissue predisposing to bradyarrhythmia through high-grade AV block (Davey, 2010).

The T wave is generated by myocardial voltage gradients during the repolarization phase of cardiomyocyte action potentials (Yan and Antzelevitch, 1998; Antzelevitch, 2006). Myocardial ischaemia may cause T wave changes and abnormally tall T waves (Rowlands, 2002). Clinical studies have shown that long QT intervals predispose people to malignant ventricular arrhythmias and sudden death (Bednar *et al.*, 2001). Prolonged QT interval is associated with blood pressure; left ventricular mass, prevalent coronary artery disease (Festa *et al.*, 2000). As clarified in table (4-5) cadmium treated group (T1) showed a significant depression in serum calcium concentration. In hypocalcaemia, the T wave morphology remains normal and QT interval is prolonged (Sype and Khan, 2005). Prolongation of the QT interval may be a consequence of an unfavorable balance between sympathetic and parasympathetic activity. It has been noted that imbalance in cardiac autonomic function (increased or decreased sympathetic activity) shortens or prolongs the QT interval of the electrocardiogram (Karjalainen *et al.*, 1997, Bednar *et al.*, 2001).

Cadmium induced decreases in both intracellular potassium and reduced glutathione concentrations (Chan and Cherian, 1992). The proposed hypokalaemia after cadmium exposure may associated with cardiac arrhythmias and prolongation of the QRS duration, and an increase in P wave amplitude and duration (Rowlands, 2002). Wide QRS complexes is a definite diagnosis of atrial fibrillation (AF) (Gulamhusein *et al.*, 1985), also a broad QRS usually reflects a disease of the right, the left or both bundle branches (Davey, 2010).

Heart rate dependency of QT interval is well known (Malik *et al.*, 2008), QT interval and heart rate, however, are highly negatively correlated with each other (Rautaharju and Zhang, 2002). Similar to the QT interval, the PQ interval and QRS width are rate dependent (Malik *et al.*, 2008).

Several mechanisms were placed on deciphering the Cd toxicity, including induces reactive oxygen species (ROS) and oxidative stress (Lopez *et al.*, 2006; Gems and Partidge, 2008). Many studies conducted in the last decade have illustrated increased biological oxidative pathways during cardiovascular disease (CVD) in animals and humans. Thus, increased production of reactive oxygen species may be a unifying mechanism in CVD progression, and antioxidants may have therapeutic

value in this setting (Wattanapitayakul and Bauer, 2001). The cardioprotective effects of vitamin E are attributed to its antioxidant properties. Vitamin E is able to extinguish single oxygen species as well as to terminate free radical chain reactions (Giugliano, 2000). In conclusion, this study showed that the Cadmium effect on electrical conduction of heart was represented by abnormality in some of ECG component as well as the protective role of vitamin E as antioxidant in the cardiovascular system was also confirmed.

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