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Research Article

Cardio-protective Effects of Bradykinin and Tetraethyleamonium on the Arrhythmia Induced by Barium Chloride in Male Rat

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Abstract | Various chemical mediators of inflammation such as serotonin, Bradykinin (BK), histamine, substance P, and ATP have been linked to the pathophysiology of multiple vascular ailments, including atherosclerosis, migraine, and myocardial infarction. Cardiovascular performance seems to be significantly regulated by BK. It is also becoming more and more recognized as a component of how medications that affect the liver, kidney, and circulation work. Tetraethylammonium (TEA), a nonselective potassium channel blocker, works as an antiarrhythmic drug in addition to inhibiting potassium channels to affect repolarization. We studied levels of heart electrical activity as well as the physiological effects of different dosages of BK and TEA administered intravenously on a cardiac arrhythmia caused by $BaCl_2$ *in vivo*. After measuring the electrocardiographic (ECG) parameters in male Wistar rats, which were anesthetized and had electrodes implanted subcutaneously into the right forelimb and left hind limb, the ECG waves and parameters were recorded and analyzed using the LabChart software and the Bio Amp of ADInstruments data acquisition system. Barium Chloride, in doses of 10 and 20 mg/kg (i.v), produced intense and persistent bradycardia associated with prolonged QTc at was observed in the ECG *in vivo* recording, if not treated after 20-25 in rats were dying. Bradykinin and TEA also produced a similar pattern of a fall in heart rate but inhibited mortality. In addition, the responses produced by TEA are of greater magnitude as compared to the BK. In conclusion, Bk and TEA produce cardioprotective activity in rats.

Keywords | Arrhythmia, Barium Chloride, Bradykinin, ECG, Heart rate, Tetraethylammonium

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INTRODUCTION

Acute myocardial ischemia and infarction are frequently the outcomes of the underlying etiology, coronary artery blockage (AMI) which is a notable cause of death in developed nations (Hundahl et al., 2017). The identification of a possible "cardio-safe" new chemical entity (NCE) depends heavily on cardiac electrophysiology in the animal model as well as in vitro and silico studies (De Clerck et al., 2002). It is well known that the infusion of $BaCl_2$ promotes the development of arrhythmia by causing prolonged depolarization and triggering activity via rises in Na^+ and Ca^{2+} influx to the heart. The presence of K^+ in the external solution may be impeded by the penetration of Ba^{2+} through the K^+ channel, which could increase the auto-rhythmicity of the heart and result in ventricular arrhythmia, according to electrophysiological investigations. This is the most important finding (Kehl et al., 2013; Rowley and Roux, 2013). The therapeutic advantages of nonapeptide BK have been demonstrated in several clinical and experimental trials, and they extend beyond the treatment of hypertension and congestive heart failure (Ozer et al., 2002). Since BK circulates at extremely low concentrations (1 to 50 fmol/mL) and is quickly digested by kininases,

therefore, primarily serves as a local hormone. Although BK acts as a counter-regulatory against the vasopressor hormonal systems such as the renin-angiotensin system (RAS), aldosterone, and catecholamines (Singh, 2020). The role of the BK in the regulation of coronary blood flow and its effects on heart disorders have been the subject of several experimental studies utilizing animal models. Local cardiac KKS is thought to play a key protective effect on the heart by postponing the onset of heart failure in conditions like myocardial infarction (Silva et al., 2022). Kallikrein gene transfer, tissue kallikrein infusion, human kallikrein overexpressing animals, B1 or B2 BK receptor knockout mice, and other techniques have all been used. According to studies, the KKS improves coronary blood flow, reduces infarct size, and prevents post-myocardial infarction left ventricular remodeling. This suggests that the KKS plays a significant role in the effects of ACE inhibition, particularly on angiogenesis and myocardial regeneration. Some of the research discussed above has also shown that the positive outcomes associated with the use of ACE inhibitors and/or angiotensin receptor blockers (ARBs) are not only due to the inhibition of Ang II generation or effects, but also in part to the prevention of BK enzymatic degradation (Xu et al., 2013; Su, 2006). Bradykinin activates the B2R in endothelial cells, causing the release of NO, prostacyclin, endothelium-derived hyperpolarizing factor (EDHF), and tissue plasminogen activator. These substances have a variety of physiological effects on the cardiovascular system, including control of vascular tone and local blood flow to organs, blood clotting, fibrinolysis, and homeostasis (Mohammed and Al-Habib, 2018). Because of its opposing effects on the activation of the angiotensin II AT1 receptor, research studies have shown that B2R has a protective role in cardiovascular function (Su, 2014). Bradykinin produces vasodilatation, has an anti-inflammatory impact, reduces ROS, inhibits fibrinolysis, and has antithrombotic properties, all in direct contrast to angiotensin II (De Clerck et al., 2002).

A straightforward quaternary ammonium compound is tetraethylammonium. It mostly functions as a potassium channel blocker. This impact mostly prolongs the duration of action potentials in excitable cells. The TEA is not permeable to the cellular membrane because of its polypeptide chains. Multiple channels respond differently to the extracellularly supplied when TEA acts from outside the cell. Under these circumstances, some channels are insensitive to TEA. Millimolar doses of TEA given to the membrane's intracellular surface can inhibit entire K channels. TEA also imitates or opposes the activities of choline and acetylcholine, two additional quaternary ammonium molecules. Blocking nicotinic receptors at the neuromuscular junction and the autonomic ganglia is an example of these activities (Furman et al., 2018). In this study, we have investigated the antiarrhythmic effects of the BK and non-selective K^+ channel blocker, TEA. An *in vivo* arrhythmia model was developed to induce ventricular bradyarrhythmia in rats.

MATERIALS AND METHODS

The curative and preventative properties of BK and TEA were observed in the current investigation. The following groups were created randomly among the experimental rats: Twenty-eight rats were randomized into four groups (I) within the control group (10 rats) that received 2 ml/kg of normal saline infusion. (II) with the administration of 7 and 20 mg/kg of $BaCl_2$; n=6. (III) with the administration of 10 and 12 mg/kg of BK; n=6. (IV) in the TEA group at 10 mg/kg; n=6. All drugs were given intravenously through the caudal vein. Before and after drug administration, baseline ECG measurements were taken for several minutes. Heart rate, RR, and QT intervals were among the ECG data that were recorded. Using Bazett's formula, the rate-corrected QT (QTc) interval was also calculated: QTc=QT/RR1/2

Experimental Design

Adult male albino rats weighed between 250 – 300 grams were used in the current project. The animals were raised and housed in plastic cages, bedding with wood pellets, in a room with a controlled temperature of 24± 3°C, in the animal house belonging to the Department of Biology, Faculty of Science, Zakho University. The animals were exposed to a 12/12 hrs. light/dark cycle throughout the experiments. The rats were provided with enough water and were fed standard rat food. The animals were allowed to adapt just before the trial. The cages used to house the rats were made of polypropylene and sized by the most recent Protocol for the Care and Use of Laboratory Animals. The cages were placed on stainless steel cage stands.

Animal Preparation

The University of Zakho's Animal Research Ethics Committee accepted the animal experimentation techniques, which complied with the "Guide for the Care and Use of Laboratory Animals" issued by the National Institutes of Health (NIH) in the United States of America. All the rats were anesthetized by administering xylazine and ketamine intravenously. To administer medication intravenously, a 24-gauge catheter was placed into a tail vein. Rats positioned on a holding board had ECG needle electrodes were placed on their forelimbs and left hind legs. The ECG signals were amplified using a digitizer (Powerlab 8/35, AD Instruments, Sydney, Australia) and an ADI amplifier Bio Amp (MLA-136). To examine the digitized data, ADI Labchart7 software was utilized. The digitized ECG was analyzed using ADI Labchart7 software, which provided

an automatic collection of data on the heartbeat rate and several normal cycles.

Statistical Analysis

The median of each result is shown together with its interquartile range. All non-parametric variables were compared using the Kruskal-Wallis test, and the findings were corrected using Dunn's test. One-way ANOVA was used to compare group averages, and the Tukey post hoc test was performed to evaluate whether there were any differences. All test data were two-tailed, and (P0.05) was used to indicate statistical significance. Beats/min are used to report resting heart rate. If there was a sudden reduction in heart rate of at least 30 beats per minute, spontaneous bradycardias were counted and characterized. The term "beats lost" is recorded as [decrease in HR (Hz) time (s)]. Additionally, we determined total bradycardia (beats lost/min), which is the sum of incidence and amplitude of bradycardia (beats lost) (min). All computations and graphics were created using Prism 7 (GraphPad analysis) (GraphPad Software, San Diego, California, USA).

RESULTS

Effect of $BaCl_2$

The effect of $BaCl_2$ at doses of (7and 20 mg/kg iv) on HR, RR, QRS, QT, and QTc are shown in (Table 1 and Figure 1). In all $BaCl_2$-treated groups, HR gradually decreased as compared with the matched saline control group. Injection of $BaCl_2$ (7mg/kg), after 15 min non-significantly decreased HR. While, after 30 min of infusion significantly decreased HR from (300.8 ± 12.13 control to 273.4 ± 7.087 and 258.4 ± 2.369), respectively. Further decrement in HR was observed after increasing the $BaCl_2$ dose to (20mg/kg) iv was notable in comparison to the 7 mg/kg of $BaCl_2$, and induced severe bradyarrhythmia, if not treated with antiarrhythmic drugs, four rats died, due to $BaCl_2$ administration. On the other hand, the period domain parameter RR interval significantly decreased at all doses of $BaCl_2$ as shown (Figure 1B, Table 1; P≤0.05 one-way ANOVA). Similarly, $BaCl_2$ at a dose (7mg/kg) i.v observed incensement in the QRS interval while showing a decrease in QRS interval at (20 mg/kg) iv as shown (Figure 1C, Table 1; P≤0.05 one-way ANOVA). Bazett's method, which adjusted the QT interval to HR, is a highly helpful tool for calculating QT. This is dependent on multiplying the square root of the RR interval by the QT interval.

To evaluate the direct effect of $BaCl_2$ on QT intervals, (7 mg/kg) of $BaCl_2$ was infused and waited for 15, 30 min for each period ECG was recorded and ECG changes were measured. The QT intervals were significantly increased in comparison to the control. However, no additional increases were observed after 30 min of infusion (0.069 ±0.035, 0.09±0.0014, 0.084±0.0012), respectively. Furthermore, a significant decrement (0.075±0.001) was recorded after 15 min of 20 mg/kg iv $BaCl_2$ treatment as compared with 7 mg/kg iv, (Figure 1D and Table 1).

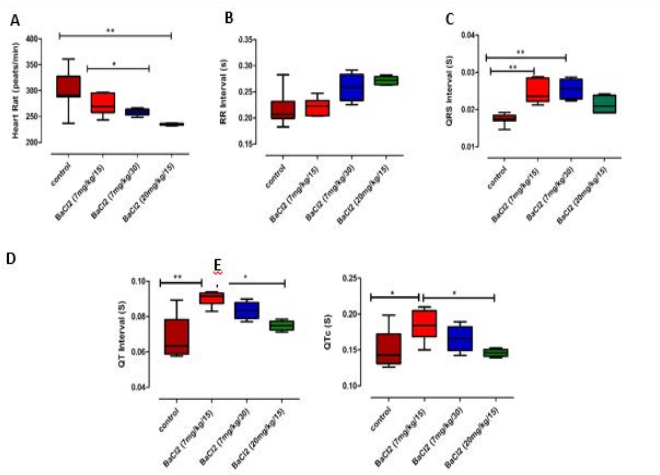

Figure 1: The effects of BaCl2 infusion (7 mg/kg for 15 and 30 minutes, and 20 mg/kg for 15 minutes) on heart rate, RR Interval, QRS Interval, QT interval and QTc Interval in male albino rats. The significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

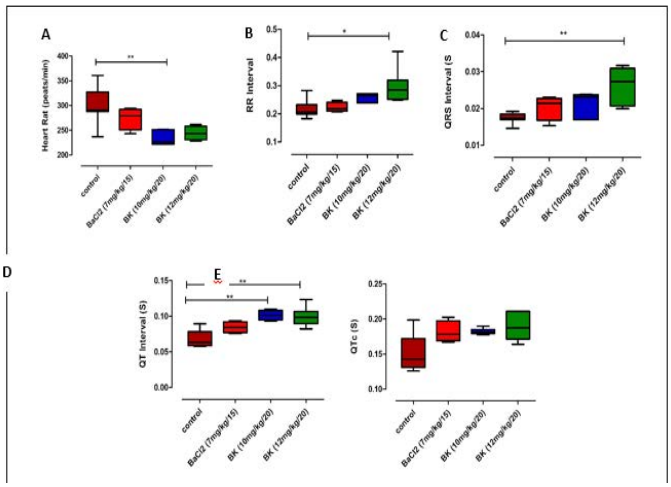

Figure 2: The effects of BK infusion (10 mg/kg, and 20 mg/kg for 20 minutes) on heart rate, RR Interval, QRS Interval, QT interval and QTc Interval in male albino rats. The significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

Effect of Bradykinin on the Rat ECG

Electrocardiograph alterations were evaluated after (10 and 12mg/kg) (iv) BK administration at 20 min intervals between each dosage to assess the direct influence of BK on amplitude and interval domain parameters. Bradykinin stimulates vasosensor reflexes and induced a significant change in HR frequency as compared with the control and the $BaCl_2$ groups. The change of HR after BK infusion

Table 1: The effects of BaCl2 infusion (7 mg/kg for 15 and 30 minutes, and 20 mg/kg for 15 minutes) on some heart parameters (Median±interquartile range) in cardiac arrhythmia in male albino rats.

Parameters	Control	BaCl2 (7 mg/kg/15min)	BaCl2 (7 mg/kg/30min)	BaCl2 (20 mg/kg/15min)
HR				
Mean	300.8	273.4	258.4	234.8
Std. Error	12.13	7.087	2.369	**0.653**
RR				
Mean	0.216	0.221	0.258	0.272
Std. Error	0.011	0.0056	0.0117	0.0028
QRS				
Mean	0.017	0.024	0.026	0.021
Std. Error	0.0004	0.0011	0.0014	0.0013
QT				
Mean	0.069	0.090	0.084	0.075
Std. Error	0.0035	0.0014	0.0012	0.001
QTc				
Mean	0.152	0.186	0.166	0.146
Std. Error	0.0074	0.0068	0.0072	0.0021

Table 2: The effects of BK infusion (10 mg/kg and 12 mg/kg for 20 minutes) on some heart parameters (Median±interquartile range) in cardiac Bradyarrhythmia induced by BaCl2 in male albino rats.

Parameters	Control	Bacl2 (7mg/kg /15)	BK (10mg/kg /20)	BK (12mg/kg /20)
HR				
Mean	300.8	274.0	233.1	244.0
Std. Error	12.13	11.15	5.854	7.065
RR				
Mean	0.216	0.223	0.258	0.278
Std. Error	0.0104	0.0087	0.0063	0.0115
QRS				
Mean	0.017	0.020	0.021	0.026
Std. Error	0.0004	0.0017	0.0014	0.0020
QT				
Mean	0.069	0.085	0.102	0.099
Std. Error	0.0035	0.0039	0.0034	0.0056
QTc				
Mean	0.152	0.182	0.182	0.189
Std. Error	0.0074	0.0076	0.0008	0.0079

decreased from (274.0± 11.15) control to 233.1± 5.854 at (10 mg/kg) iv of BK and 244.0 ±7.065 at (12 mg/kg) iv of Bk. The significant effect was at the dose of (12 mg/kg) iv of BK in comparison to the saline control group. On the other hand, the RR interval increased at both doses of BK as compared with the saline control and $BaCl_2$ groups. The mean RR interval was significant at (12 mg/kg) iv of BK infusion. While at (10 mg/kg) iv the effect was nonsignificant (Figure 2B, Table 1; P≤0.05 one-way ANOVA).

Similarly, the mean QRS interval increased in the presence of Bk at dose (10 mg/kg) iv. A Further increase was recorded at BK dose (12 mg/kg) iv, in comparison to $BaCl_2$ and control groups (0.021±0.0014, 0.026± 0.0020, 0.020±0.0017, 0.017 ± 0.0004), respectively. While at the mean QT interval the increment was more at a Bk dose (10 mg/kg) iv.

The data from the current study indicated that QTc intervals increased as compared to the control. After infusion of more BK (12mg/kg) iv further increments were observed. The change was just significant when compared with

Table 3: The effects of TEA infusion (5 mg/kg for 15 minutes) on some heart parameters (Median±interquartile range) in cardiac Bradyarrhythmia induced by BaCl2 in male albino rats.

Parameters	Control	Bacl2 (7mg/kg/15)	TEA(5mg/kg/20)
HR			
Mean	308.7	280.1	272.5
Std. Error	10.37	10.58	6.360
RR			
Mean	0.216	0.189	0.215
Std. Error	0.0104	0.0335	0.0055
QRS			
Mean	0.017	0.021	0.026
Std. Error	0.0004	0.0014	0.0007
QT			
Mean	0.069	0.085	0.087
Std. Error	0.0035	0.0029	0.0013
QTc			
Mean	0.152	0.185	0.186
Std. Error	0.0074	0.0067	0.0015

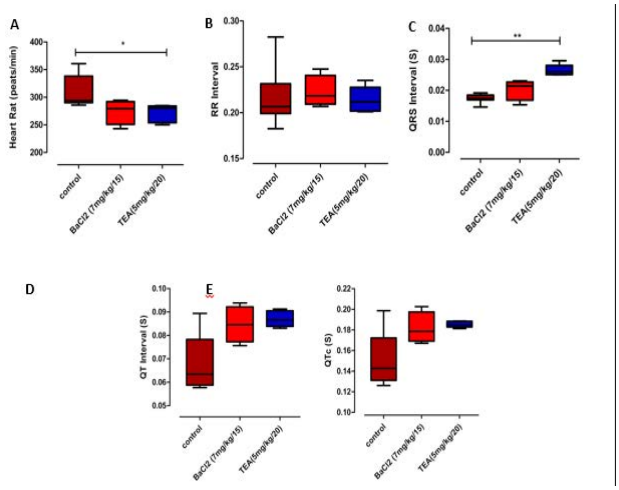

Figure 3: The effects of TEA infusion (5 mg/kg for 20 min) on heart rate, RR Interval, QRS Interval, QT interval and QTc Interval in male albino rats. The significant difference was observed between the groups. Data are expressed as Median ± interquartile range.

control (0.152±0.0074 control, 0.182±0.0076 $BaCl_2$, and 0.189±0.0079 BK (12 mg/kg) iv (Figure 2E, Table 2; P≤0.05 one-way ANOVA).

Effect of Tetraethylammonium on Rat's ECG

The results of this study indicate that changes in the frequency of the domain parameter HR with TEA were significantly different as compared with $BaCl_2$ and saline control group (Figure 3A, Table 3; P≤0.05 one-way ANOVA). Through the infusion of $BaCl_2$ for 15 minutes (i.e., before infusion of TEA), Brady arrhythmia was induced and the RR interval increased while after TEA infusion significantly decreased. The QRS after TEA infusion significantly increase compared with $BaCl_2$ and saline control group. Nearly similar means of QT and QTc for both $BaCl_2$ and TEA infusion were recorded and the response of QT and QTc in the presence of $BaCl_2$ and TEA were prolonged as compared to the control (0.085±0.0029 $BaCl_2$, 0.087±0.0013 TEA, 0.069±0.0035 control) and (0.185±0.0067 $BaCl_2$, 0.186±0.0015 TEA, 0.152±0.0074 control) respectively.

DISCUSSION

Previous research from our group (Mohammed et al., 2022) and others has shown that the Wistar rat's heart rate on average is between 350 and 370 beats per minute (bpm). Infusion of Saline solution in control tests causes no appreciable changes, ruling out the likelihood of ischemia/stretch-induced reactions on the artery wall (Singh et al., 2020). In the present study, $BaCl_2$-induced animal models of ventricular arrhythmia were established to investigate and compare the protective effects of BK at different concentrations and TEA on ventricular arrhythmia. The results demonstrated that both BK and TEA significantly decreased heart rate and prolonged the QTc intervals and altered other ECG parameters. If the animals left untreated by BK and TEA died in every case within 20–25 minutes. Therefore, when TEA and BK were used as medical treatments, despite severe bradycardia and a heart rate reduction to 233 bpm after intravenous treatment, the sinus rhythm was completely restored. Meanwhile, such two drugs showed comparable therapeutic and protective impacts on arrhythmias brought on by $BaCl_2$.

In injured individuals, cardiac arrhythmias are a major

cause of mortality. Particularly concerning is the possibility of patients dying without timely and adequate medical attention when significant arrhythmias progress very quickly. There are two types of arrhythmias, bradyarrhythmias, which are slow, and rapid (tachyarrhythmias). Bradyarrhythmias include nodal rhythms, sinus bradycardia, and all types of heart block. Blocking K channels causes bradycardiaprolonged reprepolarization the lengthening of the QT interval (Thomas, 2000). The above results may be mainly explained by the K^+ channel blockade of terfenadine and amiodarone, and partially attributed to the Na^+ and Ca^{2+} channel blockade by these two drugs (Liu et al., 2014).

The previous study showed that IKr channel blockers have a dominant effect on bradycardia, according to QT/RR plots (Liu et al., 2009). Additionally, Ghasi et al. (2009) demonstrated that 3 mg/kg of $BaCl_2$ administered intravenously was sufficient to cause ventricular arrhythmia in dogs, and it was discovered that $BaCl_2$ at doses 12.5 mg/kg and 15 mg/kg was necessary to cause ventricular tachycardia in rats. On the other side, an intravenous (jugular vein) injection of barium chloride (20 mg/kg) was used to cause ventricular fibrillation. As a result, species differences in the cardiotoxicity response to $BaCl_2$ may be responsible for that (Ghasi et al., 2009). Regarding ionic fluxes, the impacts of Ba^{2+} on the heart and other excitable membranes can be attributed mainly to a decreased K^+ outward diffusion from the cell without a corresponding drop in the actively transmitted input, that is the inward rectifier protein (Salihi et al., 2017). Preventing a significant repolarizing potassium current in the heart IKr is thought to be the main framework by which potassium channel-blocking drugs, whether "pure" or "mixed," prolong the QT interval (Roden, 2006).

According to the findings of the current investigation, BK injection into the tail vein causes rapid, transitory hypotensive reactions but prevents mortality induced by $BaCl_2$- bradyarrhythmia. Similar patterns of reactions are also elicited by TEA, associated with a decreased HR. Additionally, compared to $BaCl_2$, the hypotensive responses generated by BK are more powerful than TEA. This is explained by BK's ability to protect the heart. Such an outcome was consistent with recent research that showed endogenous allergens play a second cardioprotective action in acute inflammation by reducing heart rate during acute inflammation (Revand and Singh, 2021; Roy et al., 2022). This result may attribute to the NO production by cardiomyocytes because the parent peptide BK-(1-9) is known to induce NO production in cardiac myocytes (Oldenburg et al., 2004; Semis et al., 2019) and may contribute to cardiac pre-conditioning (Heusch et al., 2015). The concentration-response curve supports BK fragments' role in stimulating NO generation. These *in vitro* findings collectively indicate that the examined BK segments were biologically active in promoting NO generation and that these actions were almost certainly triggered by signal transduction (Singh, 2020; Silva et al., 2022). The majority of the *in vivo* cardiovascular impacts of kinins, involving endothelium-dependent vasodilatation, smooth muscle contraction in the lungs and blood vessels, and enhanced vascular permeability, seem to be mediated by the B2 receptor (Jean, et al., 2016). While endotoxin, pro-inflammatory cytokines, tissue injury, inflammation, anoxia, and myocardial infarction all cause B1 receptor activation, these events also cause them to operate in a specific way (Kopylov et al., 2016). One important mechanism for this vasodilation is BK-stimulated NO generation, which is at least partially mediated by eNOS phosphorylation (Blum-Johnston et al., 2013).

The cardioprotective effect of the TEA injection was shown in this study by alterations in HR variability. Additionally, the amount of Brady- arrhythmia caused by $BaCl_2$ infusion was decreased, and rat mortality was inhibited within 20–25 minutes. It is believed that a molecule of TEA physically enters the pore, blocks the K channel, and stops bradyarrhythmia's rat mortality. This outcome is related to the various TEA-induced activities. Tetraethylammonium inhibits potassium channels that are triggered by calcium and have a high conductance. Additionally, partially offset the noradrenaline release reduction that is thought to inhibit calcium permeability. In contrast, TEA generated its influence by repressing the potassium current, thus also prolonging the electrical impulses and the period during which Ca^{2+} ions can access noradrenergic nerve terminals. Tetraethylammonium facilitated the discharge of noradrenaline at all calcium concentrations in the perfusate (Häusler et al., 1979).

The restrictions of current ECG recording techniques in small animals as such rats can affect the electrophysiological variables. For instance, some techniques need anesthesia, while others call for invasive procedures to install ECG electrodes. The heart rate (HR), rhythm, different segments, and intervals of the ECG may be impacted by surgical operations and anesthesia by drugs (Kumar et al., 2017). In addition, the sedated rat's ECG recording lacks validity for the HR variability study (Fateev et al., 2012; Castiglioni et al., 2013).

CONCLUSION

The cardiovascular system's pharmacological antiarrhythmic actions of BK and TEA are discussed in this paper. The investigated substance had therapeutic antiarrhythmic action in bradyarrhythmia produced by $BaCl_2$. According

to our results, BK and TEA prevented the bradycardia caused by $BaCl_2$ that caused death. TEA is more effective than BK at inducing a cardioprotective action by reducing the severity of bradyarrhythmia. The heart rate does, however, slightly raised with a higher dose of BK.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

NOVELTY STATEMENT

This study examined the levels of heart electrical activity along with the physiological effects of different dosages of BK and TEA on an in vivo cardiac arrhythmia induced by BaCl2.

AUTHORS CONTRIBUTION

In the present study, the author is responsible for study conception, design, data collection, analysis, and interpretation of results, as well as preparing the manuscript.

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