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Effect of Intravenously Injected Arachidonic Acid on Electrocardiography in Rats

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Abstract

Arachidonic acid (AA), which is released from phospholipids in the cell membrane by a variety of stimuli, has physiological and pathophysiological roles in the cardiovascular system. The current study was designed to determine the effect of intravenously (iv) injected AA on the electrocardiography (ECG) of the anesthetized rats.

The ECG waves obtained from the lead II were written by placing electrodes on limbs of the ketamine and xylazine mixture (50 mg/kg/20 mg/kg; im) in anesthetized adult Spraque Dawley rats. AA (3 mg/kg; iv) statistically significantly ($p<0.05$) caused to prolong of the ECG waves and intervals, resulting in a decrease in the heart rate of the rats.

The current findings herein present the effect of the most abundant endogenous unsaturated fatty acid AA on ECG. The results clearly showed that AA could produce to bradycardia response by increasing the ECG waves and interval durations.

Keywords: Arachidonic acid, Electrocardiography, Intravenous, Heart rate.

Introduction

Arachidonic acid (AA) is the most common polyunsaturated fatty acid in the body. In response to various physiological and pathological stimuli, it is released from cell membrane phospholipids under the effect of phospholipase enzymes and is metabolized by cyclooxygenase (COX) and lipoxygenase (LOX) pathways into many biologically active products in the body.[1] AA and its metabolites have a role in the cardiovascular homeostasis.[2] In the peripheral, AA and its metabolites cause the relaxation in vascular smooth muscle, including coronary arteries.[3-5] It was reported that iv injection of AA caused first a rapid fall of arterial pressure followed by a brief rise and a subsequent prolonged fall.[6] The same report also indicated that peripherally injected AA decreased the heart rate of the rats along with its blood pressure effect.[6] In another report, that intravenously injected AA produced a dose-dependent fall in blood pressure in normotensive and spontaneously hypertensive rats was showed.[7] Moreover, central administration of the AA has many autonomic potentials including being able to affect the cardiovascular system.[8,9] We previously reported that intracerebroventricular injection of AA caused the pressor and bradycardic responses in normotensive rats by activating central COX[8] and LOX[9] pathways.

Although the previous reports explain that AA has a potential role on blood pressure and heart rate as cardiovascular parameters, there is no clear report about the effect of AA on electrocardiography (ECG), reflecting the electrical activity of the heart. Therefore, the purpose of the present study was to investigate the role of iv AA injection on the ECG waves.

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Material and Methods

3-4 months old, having 275-325 g body weight, 10 Sprague–Dawley rats were used in the experiments approved by The Animal Care and Use Committee of Bursa Uludag University (2020-03/05).

In the study, animals were used individually under ketamine/xylazine (50 mg/kg 20 mg/kg; im) mixture anesthesia. The electrocardiogram (ECG) was measured at leads II level in the anesthetized rats by using the MP36 system and the AcqKnowledge software (BIOPAC Systems Inc.). For this reason, ECG electrodes (SS2L, BIOPAC Systems Inc. California, USA) were inserted limbs of rats. The P and the T waves duration, the QRS complex duration, and the P-R, the Q-T and the R-R intervals duration were used as ECG parameters in the present study. The heart rate (HR) of the rats was calculated by using the R-R intervals duration formula.

The animals were divided into 2 groups which included 5 rats in each group, as control and experimental groups. The animals in the control group and experimental group were treated with saline (1 mL/kg; iv) and AA (3 mg/kg; iv), respectively, via the tail vein of the rats. After the treatments, the ECG of the rats was recorded for 60 min. AA purchased from Sigma-Aldrich Co. (Deisenhofen, Germany) was freshly solved in saline on the day of the experiment. The dose of AA was chosen from the previous study.[7]

Sigma Stat 3.5 software (CA, USA) was used for the statistical analysis of data. For Statistical analysis, repeated-measures analysis of variance (ANOVA; two-way) and the post-ANOVA test of Bonferroni were preferred. The data given as mean ± standard error of the mean (SEM) in the graphs were considered significant at $p<0.05$.

Results

Before the treatments, the P wave duration (Fig. 1A), the T wave duration (Fig. 1B), the QRS complex duration (Fig. 1C), the P-R interval duration (Fig. 1D), the Q-T interval duration (Fig. 1E), the R-R interval duration (Fig. 1F), and HR (Fig. 2) baseline levels of the anesthetized rats (n=10) were measured as 0.025 sec, 0.052 sec, 0.022 sec, 0.052 sec, 0.070 sec, 0,290 sec, and 226 bpm, respectively.

It was observed that iv injected AA group animals (n=5) had an increase in the P wave duration (Fig. 1A), the T wave duration (Fig. 1B), the QRS complex duration (Fig. 1C), the P-R interval duration (Fig. 1D), the Q-T interval duration (Fig. 1E), and the R-R interval duration (Fig. 1F) when compared to the control group animals (n=5). The maximum delayed effect was observed as 0.001 sec for P wave duration (Fig. 1A), 0.0102 sec for the T wave duration (Fig. 1B), 0.0012 for the QRS complex duration (Fig. 1C), 0.0011 sec for the P-R interval duration (Fig. 1D), 0.0102 sec for the Q-T interval duration (Fig. 1E), and 0.026 sec for the R-R interval duration (Fig. 1F). Also, iv injected AA caused a decrease in HR (Fig. 2) of the anesthetized rats (n=5). The maximum bradycardic effect was detected as 12.4 bpm for HR (Fig. 2) While iv injected AA caused to prolong the rate of the electrical activity of the heart, it failed to change in the ECG waveforms, amplitude, and also isoelectric line.

Discussion and Conclusion

The obtained findings demonstrated that iv administered AA caused a decrease in HR of the anesthetized rats by increasing the P wave duration, the T wave duration, the QRS complex duration, the P-R interval duration, the Q-T interval duration, and the R-R interval duration.

ECG presents an important understanding into the functional and structural characteristics of the myocardium by reflecting the electrical activity of the heart. Action potential of heart generating in the sinoatrial node, like a natural pacemaker of the heart, reaches ventricular cardiomyocytes through subsequently the atrioventricular node, His bundle, His bundle branches, and Purkinje fibers. An ECG record includes P wave, QRS complex, and T wave which have been reflecting atrial depolarization, ventricular depolarization, and ventricular repolarization, respectively.[10,11] Findings showed that IV injection of AA increased the duration of the waves and the intervals without changing the ECG waveforms, amplitude, and also isoelectric line. The increased duration in the waves and intervals with AA injection caused the bradycardia overall in the heart. It is well known that sympathetic and vagal nerves have chronotropic, inotropic, and dromotropic effects in the heart to provide heart rate homeostasis.[12] It was reported that activation of the COX pathway of AA had a potential role in the attenuation of sympathetic influences on the heart.[13] That the attenuation of sympathetic influences on the heart with AA created bradycardia by producing chronotropic and dromotropic effects could explain the findings. In addition, stimulation of the sympathetic nervous system causes an increase in intracellular Ca^{2+} and an increase in the contraction of both atria and ventricles due to the inotropic effect.[14] Attenuation of sympathetic stimulation by AA may also cause the weakening of L-type voltage-gated calcium channel activity.

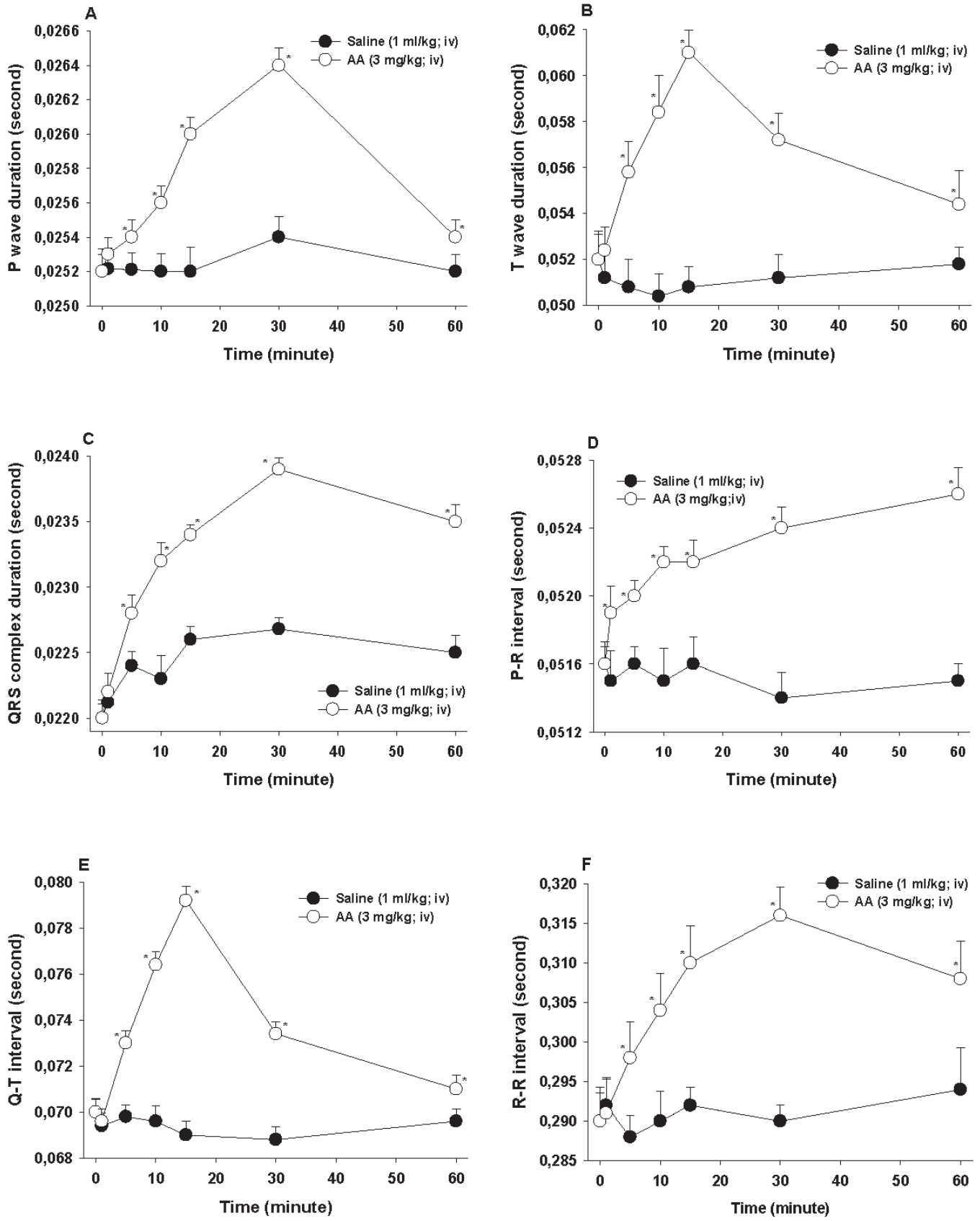

Figure 1. Effect of iv injected AA on ECG waves and intervals duration in the anesthetized rats. Saline (1 ml/kg; n=5) or AA (3 mg/kg; n=5) was iv injected to the rats. After injections, ECG was monitored for the next 60 min. The duration of the P wave (A) the T wave (B), the QRS complex (C), the P-R interval (D), the Q-T interval (E), and the R-R interval (F) measurements were obtained from the ECG. Statistical analysis was performed using two-way RM-ANOVA with a post hoc Bonferroni test. *$p<0.05$, significantly different from the value of the saline-treated group.

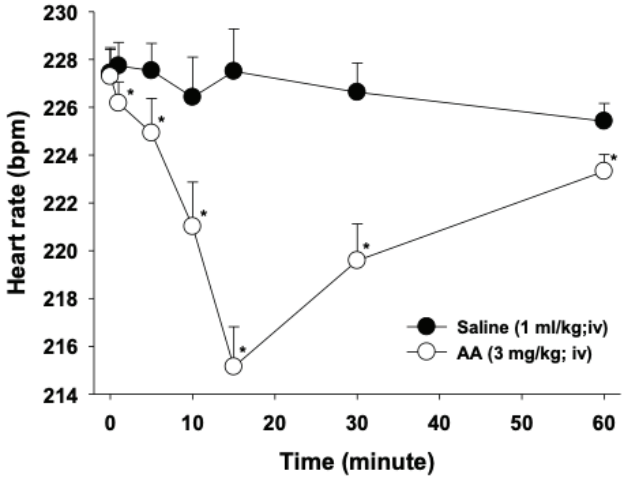

Figure 2. Effect of iv injected AA on HR in the anesthetized rats. Saline (1 ml/kg; n=5) or AA (3 mg/kg; n=5) was iv injected to the rats. After injections, ECG was monitored for the next 60 min. HR measurements obtained from the ECG. Statistical analysis was performed using two-way RM-ANOVA with a post hoc Bonferroni test. *p<0.05, significantly different from the value of the saline-treated group

Previous reports about the effect of AA on heart rate was contradictive. It was shown that IV AA injection in anesthetized rats caused bradycardia in accordance with our findings.[6] Another study reported that AA caused an increase on heart rate in the isolated perfused rat heart.[15] The contradiction may arise from the response of the organism as a whole since there was no neural control on the heart in the study made in heart rate on the isolated perfused rat heart. The neural control of the heart with sympathetic and parasympathetic neurons is more effective on the heart rate than the local mechanisms that affect the heartbeat. Moreover, it is known that AA decreases the sympathetic neural activity on the heart.[13]

AA, as an active cardiovascular neuromodulator is plenty in the central nervous system and also has roles on various autonomic controls.[16] The exogenously central injection of AA causes pressor and bradycardic responses through the COX[17] and LOX[9] pathways. Moreover, centrally injected AA-evoked pressor and bradycardic responses were mediated by COX metabolites such as TXA_2,[17] PGD, PGE, and $PGF_{2\alpha}$.[18] It is known that AA is able to cross the brain-blood barrier.[19] AA-induced bradycardia due to the delay in waves and intervals of the ECG observed in the findings may also be due to the central effect of AA by crossing the blood-brain barrier.

In summary, the present findings suggest that iv administration of AA produces prolong the rate of the electrical activity of the heart by increasing the duration of the ECG waveforms without affecting the amplitude and isoelectric line. As a result of the prolonged time of ECG waveforms, iv injected AA leads to the bradycardic response. The bradycardic response caused by AA may be due to the fact that AA may directly affect the heart or indirectly activate the central nervous system.

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