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ORIGINAL ARTICLE

Carvedilol Effects on ECG and Heart Fractional Shortening in Dog

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ABSTRACT

Carvedilol is non-selective beta blocker/alpha-1 blocker indicated for hypertension and cardiomyopathy treatment in humans. Despite numerous studies on effects of carvedilol in medical practice, there is a little information available for small animal medicine. The aim of this study was to evaluate carvedilol therapy on the electrocardiogram and fractional shortening in dogs.In this study, nine stray dogs with heart disease were involved. After preparation, ECG and fractional shortening was obtained and any abnormalities in cardiac conductive system and fractional shortening were determined. 3 hours after carvedilol (0.75 mg.kg^{-1} BW) administration, electrocardiography was taken and for assessment of fractional shortening ultrasound examination was performed immediately after admission ECG. A week after initial administration, the dogs were treated with 1.5 mg.kg^{-1} (High normal dose) and 3 mg.kg^{-1} (Toxic dose) of carvedilol and tested with electrocardiogaraphy and fractional shortening. The results indicated that in all dogs the drug reduced fractional shortening and also caused first degree block and sinus arrest. Nevertheless, the results of ECG just had a negative effect on heart rate. According to results it seems this medication can be used to treat dogs with acute hypertension, but nonetheless it is felt using of this drug requires further evaluation in long-term.

Key words: *Carvedilol, Electrocardiogram, Heart fractional shortening, Dog.*

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INTRODUCTION

High blood pressure (HBP) is a syndrome that can be caused by various reasons, but hypertension (HT) itself is a disease. High blood pressure may eventually lead to HT. Unlike medicine, in veterinary medicine, hypertension is commonly associated with causative disease [1; 2].

The first symptom of hypertension is tachycardia in veterinary medicine; however, measuring blood pressure with sphygmomanometer or Doppler method should be preformed. Systolic blood pressure above 160 mm Hg and diastolic blood pressure over 100 mm Hg considered high blood pressure in dogs and cats in relaxed situation [1]. High blood pressure medication includes using diuretics, adrenergic blockers, angiotensin converting enzyme inhibitors and calcium channel blockers.

Carvedilol is nonselective beta-blocker which also blocks alpha receptors. It used to treat mild to severe congestive heart failure. Furthermore, compared with other beta-blockers carvedilol has lowest agonist activity. This indicated that carvedilol has less negative inotropic and chronotropic activity effects in comparison with other beta-blockers which could potentially improve the clinical symptoms of heart failure. By blocking β1, β2 and also α1 receptors carvedilol can bring down blood pressure without reflexive tachycardia. As result of blocking α1 receptors, vessels are dilated, total peripheral vascular resistance decreases and despite blocking of beta receptor in heart muscle, stroke volume and cardiac output remained constant or even increased. Also carvedilol can inhibit lipid peroxidation in myocardial cells, inhibits super oxide anion, have anti-oxidant activity approximately 10 times more than vitamin E, takes effect on cardiac action potential and slightly increases duration without affecting the other parameters. For reducing mortality rate, it is used in patients in acute phase of myocardial infarction with

fractional shortening less than 40% of left ventricle. Carvedilol has greater beta-receptor antagonistic effects in comparison with older drugs [3-7]. Treatment with carvedilol significantly reduces left ventricle (LV) mass, improves LV geometry, and decreases mitral regurgitation in patients with chronic heart failure [4; 8].

There are lots of information about carvedilol in medicine, however there are a little evidence about the effects of carvedilol in veterinary medicine [1; 9; 10]. A study on turkeys demonstrate desired effects of carvedilol on cardiac cell apoptosis and improves cardiac function in patients with congestive heart failure in long-term use of this drug [6]. According to beta-blockers effects on reducing heart rate, the ability of AV blocking and severe drop in blood pressure, short-term effects of carvedilol to adjust safe dosage in dogs suffering from heart failure are required further considerations [11]. The aim of this study was to investigate the effect of carvedilol therapy on the electrocardiogram and fractional shortening in dogs suffering from congestive heart failure.

MATERIALS AND METHODS

9 stray dogs selected across from other patients which referred to veterinary Clinic of Tabriz Azad University with symptoms of heart failure. Patients included 3 female and 6 male dogs, aged between 2 to 6 years old. Blood cell counts were preformed and dogs with clinical symptoms of infectious diseases were deposit from study. After getting used to new environment, heart fractional shortening and ECG (as control) were taken and congestive heart failure confirmed. Physical restraining were used because of tranquilizers effects on ECG and heart fractional shortening [1]. Even after while physical restraining didn't need. According previous study 3 hours after carvedilol oral administration peak pharmacological effects can achieved [10]. 3 hours after administration with 0.75 $mg.kg^{-1}$ (low normal dosage) (First dose) echocardiogram and heart fractional shortening test were done by ultrasound machine (esaote pie medical) afterwards ECG was done immediately. Half life of carvedilol is about 12 to 16 hours so a week after first administration (wash out time), 1.5 $mg.kg^{-1}$ (high normal dosage) (Second dose) and a week after second administration, 3 $mg.kg^{-1}$ (toxic dosage) (Third dose) administered and similar tests also preformed.

5 MHz M-mode ultrasound probe were used for measuring heart fractional shortening. After observing cardiac papillary muscle and echocardiography, heart fractional shortening were measured with formula as follow:

$$\frac{\text{The diameter across a ventricle at the end of diastol} - \text{The diameter across a ventricle at the end of systole}}{\text{The diameter across a ventricle at the end of diastol}} \times 100$$

ECG test was obtained by Siemens Co made electrocardiogram machine in lead II due to its standardization of heart studies.

The results analyzed using SPSS software 17. The quantitative data obtained were expressed as mean ± S. D. and statistical comparison among groups were performed by one way analysis of variance (ANOVA) followed by Duncan post hoc. $P < 0.05$ was considered statistical significance.

RESULTS

Echocardiograph findings:

Results of heart fractional shortening have shown in figure 1. It seems carvedilol had negative effect in heart fractional shortening and contractility in dogs. Mean relative fraction was significantly ($P < 0.05$) decreased after 1.5 $mg.kg^{-1}$ administration of carvedilol compared with control group.

Electrocardiographic findings:

As mentioned, lead II used for electrocardiographic investigation. It is standardized for dogs and cats PQRS is positive in it.

P wave amplitude: (Hodode 0.4 mv bayad bashad)

Carvedilol effects on P wave amplitude have shown in figure 2. It seems carvedilol had no positive or even negative significant effect on the P wave amplitude thus on atrial contraction power.

P wave duration:

Carvedilol effects on P wave duration have shown in figure 3. It seems carvedilol had no significant effect on the P wave duration thus on atrial contraction duration. As results showed carvedilol have little and none significant effects in atria function.

P-R Interval:

Though little increase has seen in treatment groups but it was not statistically significant. Changes in P-R interval in control and treatment groups with various doses have shown in figure 4.

QRS Interval:
No Statistically significant changes have seen in QRS interval in normal and carvedilol treatment groups as presented in figure 5.

R wave amplitude:
Carvedilol effects on R wave amplitude have shown in figure 6. It seems carvedilol had no positive or even negative significant effect on the R wave amplitude thus on ventricular contraction power (especially the left ventricle).

Q-T Interval:
No Statistically significant changes have seen in Q-T interval in normal and carvedilol treatment groups as presented in figure 7.

Heart rate (R-R interval):
Carvedilol effects on heart rate (R-R interval) have shown in figure 8. According to the results it seems carvedilol had negative effect on heart rate and increased the R-R interval. Mean R-R interval was significantly ($P < 0.05$) increased in first, second and third groups compared with control group.

DISCUSSION

One of the most common diseases in humans and companion animals is cardiovascular diseases especially in dogs and cats. As they have similar pathogenesis with human; therefore human drugs can be utilized in treatment [1]. In the other hand most of new developed human cardiovascular drugs are tested in dogs and cats before human utilize. In several researches carvedilol has been used in treatment of heart failure, especially those associated with an enlarged heart [1; 6; 8; 12; 13]. Some papers indicated using carvedilol in heart disorders which is occurred due to cardiac muscle disorders in veterinary medicine [1; 6; 14; 15].

The effects of this drug have been studied as an anti-oxidant and anti-apoptotic drug by several papers [4; 6; 16]. In some articles this drug is used as an anti-hypertensive drug [8; 10; 14] and ultimately, it has been observed that in addition to the positive effects of this drug in the treatment of human disease and alleviate disease severity, it also has an effects on longevity [8; 10; 14].

In present study, ECG obtained before and after carvedilol administration. Results of P amplitude, P duration, R amplitude, QRS duration, duration of P-R interval, Q-T duration and R-R interval were measured in lead II, due to its standard values. Also carvedilol effects in different doses were studied on heart fractional shortening.

According to the results there was no apparent increase or decrease in P wave height and P wave duration. It has not been observed any significant differences between different doses and ECG before prescribing medication. Hence, according to the results there is no evidence that this drug has effect on time and atria performance even in increasing doses which have severe effects on cardiac function. So, it can be concluded that this drug don't have effect in atrial function even at very high doses (doses at least 4 times). These results are consistent with results of previous studies [4; 6; 10; 15].

Contradictory reports are available about the effects of carvedilol [15] and also in veterinary medicine a few articles are available about the function of carvedilol on dogs heart [6; 10]. Some articles discussed about the effects of carvedilol on blood pressure and its effects on cardiac cells function and cardiac purkinje fibers [8-10; 14; 17]. Nevertheless, the effect of this drug on fractional shortening in dogs has not been studied. Thus, the results of present study can be useful for identifying the effects of this drug on cardiac function, fractional shortening and changes in the hearts of dogs.

Effects of carvedilol on SA node and thus on cardiac function have been obviously in contrast to its effects on atrium. Accordingly in the most ECG sinus block or sinus arrest were observed. In a study on dogs it has determined that carvedilol can affects heart rate [18]. The heart rate-lowering effects in humans have been documented in studies [4; 16; 19] and considering the results of present study reducing heart rate with carvedilol in normal dose or increased doses is meaningful, which is consistent with available researches [4; 16; 19-21]. Due to beta blockers effect in heart, the effects of carvedilol in reducing heart rates can be explained. Beta-blockers are negative chronotropes and by blocking beta receptors in heart reduce cardiac rhythm and eventually modulate blood pressure. This mechanism could be used to improve heart function in patients suffering from hypertension and heart failure. Moreover, carvedilol blocks α1 receptors that lead to vasodilatation and decrease cardiac after load [4; 19; 22].

One of the important points about carvedilol is that, it decreases heart rate just by affecting SA node and not the other ways such as increasing heart refractory time, blocking AV node or interaction with ventricles (QT interval). In present study, there have been no significant changes in P-R interval and Q-T interval that demonstrates exclusive effect of the drug on SA node which needs further investigation. Therefore, if Carvedilol was affects AV node, it should be easily identified by this research because

according to the results, even at higher and toxic doses no significant changes were observed in P-R interval.

There are no other significant changes in electrocardiography data. Thus, it can be concluded that carvedilol with exception effect on heart rate, does not make other changes of electrocardiography in dog's heart. Nonetheless, this point should be kept in mind that all of dogs included have had chronic heart failure and showed symptoms of first degree block. But on the other hand, the effects of this drug on healthy heart are still in the zone of ambiguity. In our study we considered effects of drug in emergency situation but it requires long-term effects study.

Results of echocardiography have shown that significant reduction in heart fractional shortening (FC) happened in different doses of carvedilol. This reduction could be as result of relaxation and decreased cardiac contractility. As seen in formula, It can be concluded that changes in diameter across a ventricle at the end of systole will distinct heart fractional shortening because changes in diameter across a ventricle at the end of diastole is fixed in numerator and denominator.

Fractional shortening (FS) =

$$\frac{\text{The diameter across a ventricle at the end of diastol} - \text{The diameter across a ventricle at the end of systole}}{\text{The diameter across a ventricle at the end of diastol}} \times 100$$

Carvedilol decreases ventricular muscles contractility power so it can cause fractional heart shortening. Significant changes occurred between second dose compared with controlled group. This difference was not significant between third dose and control group, which illustrate that increasing doses due to compensatory mechanisms can overcome drug effects.

There isn't any research about Fs effects of carvedilol in dogs; therefore it cannot be evaluated with the findings of other investigators. If cardiac contractility decreasing effects will confirm in dog, negative inotrope effects of carvedilol on heart can also be considered as a beta blocking agent. A study has been carried out by Oyama et al [15] have shown that despite lowering effects of dopamine and dobutaminein received patients by carvedilol, it has no effect on cardiac fractional shortening that this matter is in contrast to the results of our study. On the other hand, it should be noted that firstly, the positive inotropic and chronotropic drugs have been used in that study and secondly, 0.8 $mg.kg^{-1}$ of body weight has been used. Thus, if carvedilol affects on FS can be confirmed, negative inotropic effects also will be added to its properties, which comprehensive studies should be done on dogs because in heart failure patients appropriate pumping and increased heart contractility is required.

With reference to results of present study it can be concluded that carvedilol is a blood pressure lowering agent in dogs which reduces heart rate and it can be used in dogs emergency cases for reduction of blood pressure; nonetheless, it requires further investigations to prove drug's negative inotropic effects.

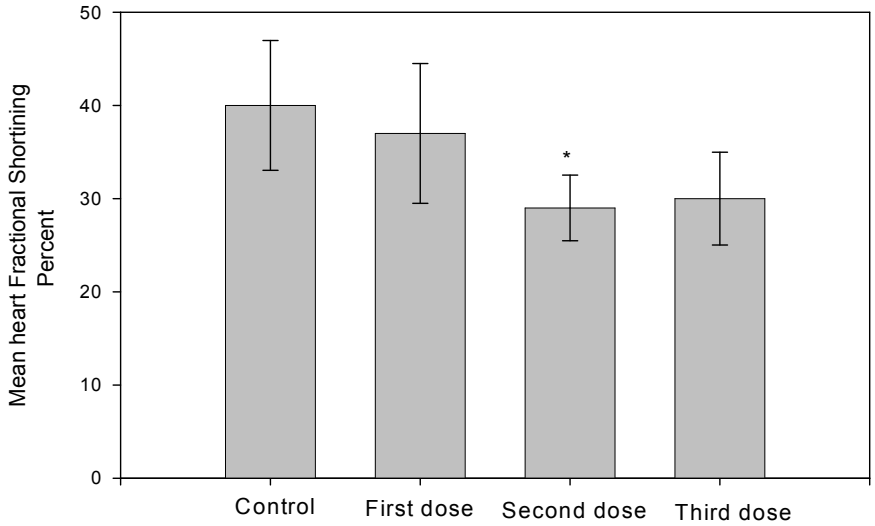

Figure-1: Echocardiography results of carvedilol in dogs. Heart fractional shortening in control, 0.75 $mg.kg^{-1}$ (First dose), 1.5 $mg.kg^{-1}$ (Second dose) and 3 $mg.kg^{-1}$ (Third dose) groups. Each value represents Mean ± S.D. (n = 9). Asterisks symbol indicate cases with $P < 0.05$ in comparison with the control group.

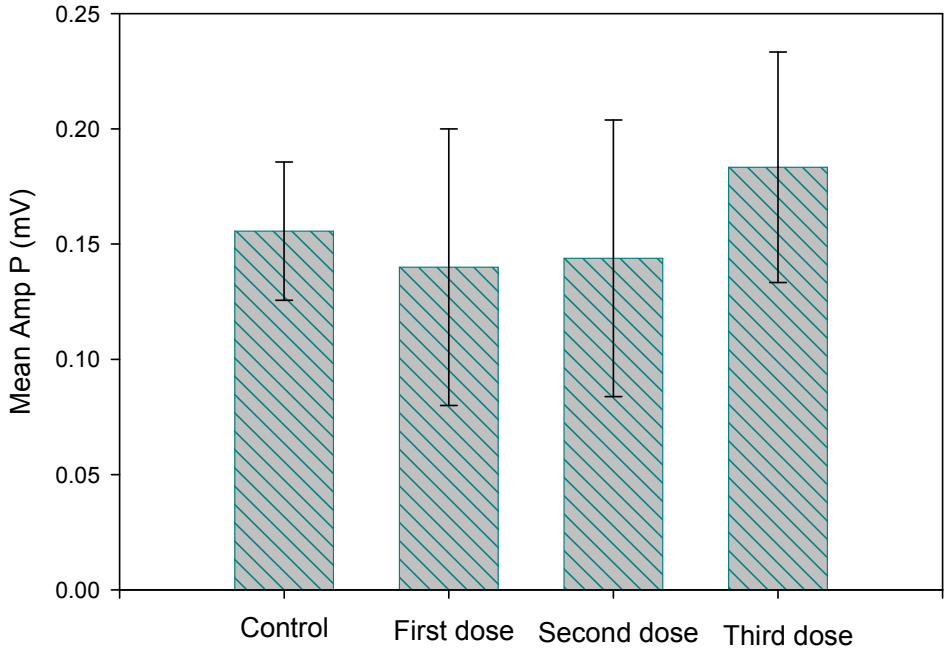

Figure - 2: Effects of carvedilol on P wave amplitude in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9).

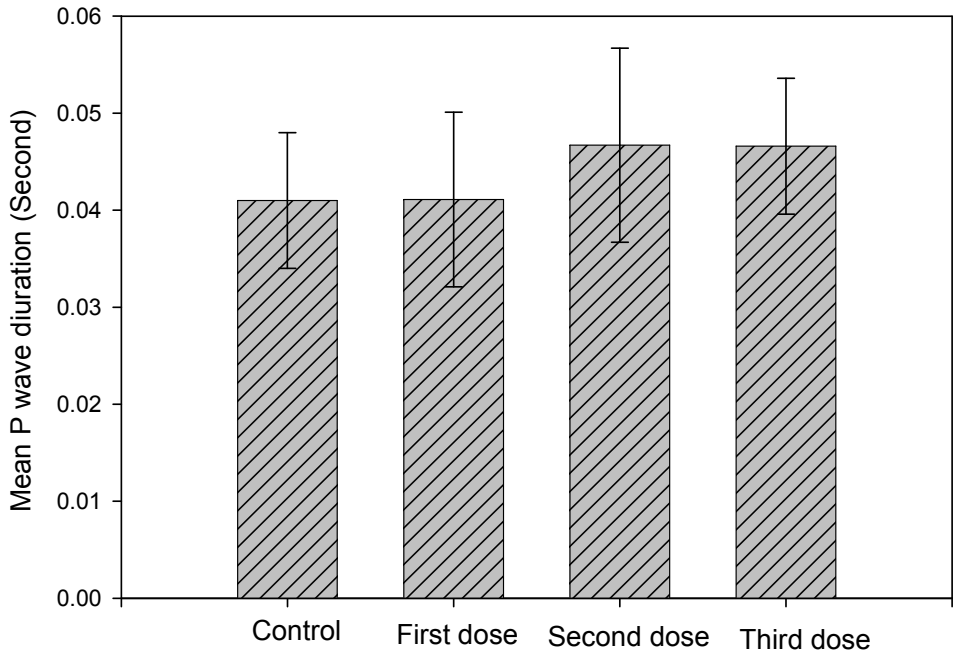

Figure - 3: Effects of carvedilol on P wave duration in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9).

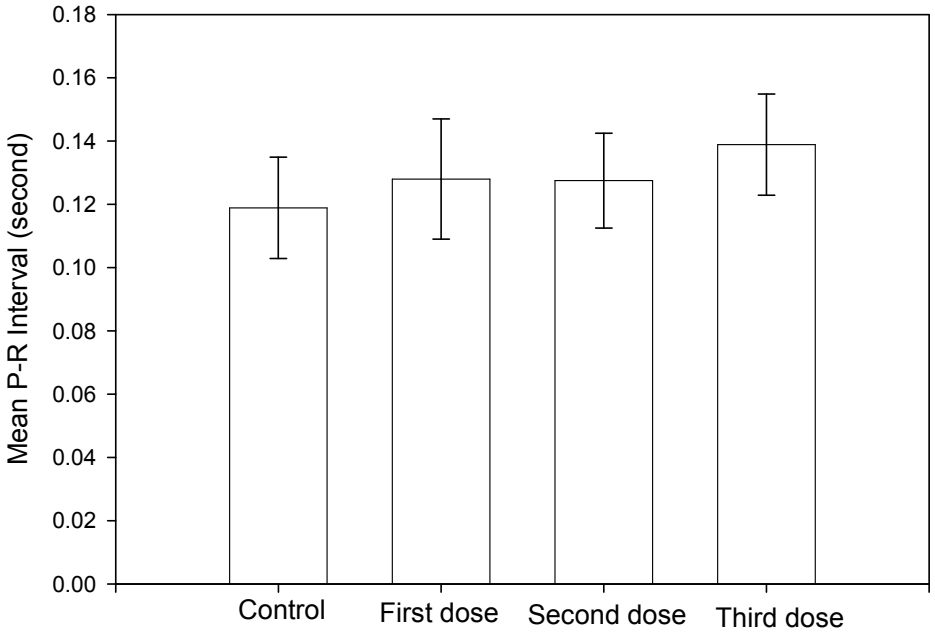

Figure - 4: Effects of carvedilol on P-R interval in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9).

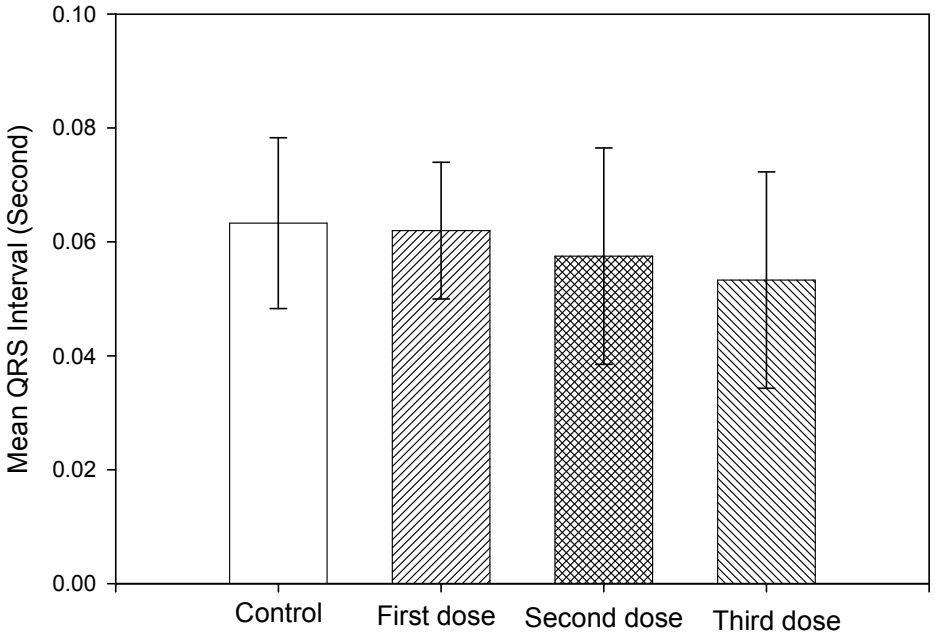

Figure - 5: Effects of carvedilol on QRS interval in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9).

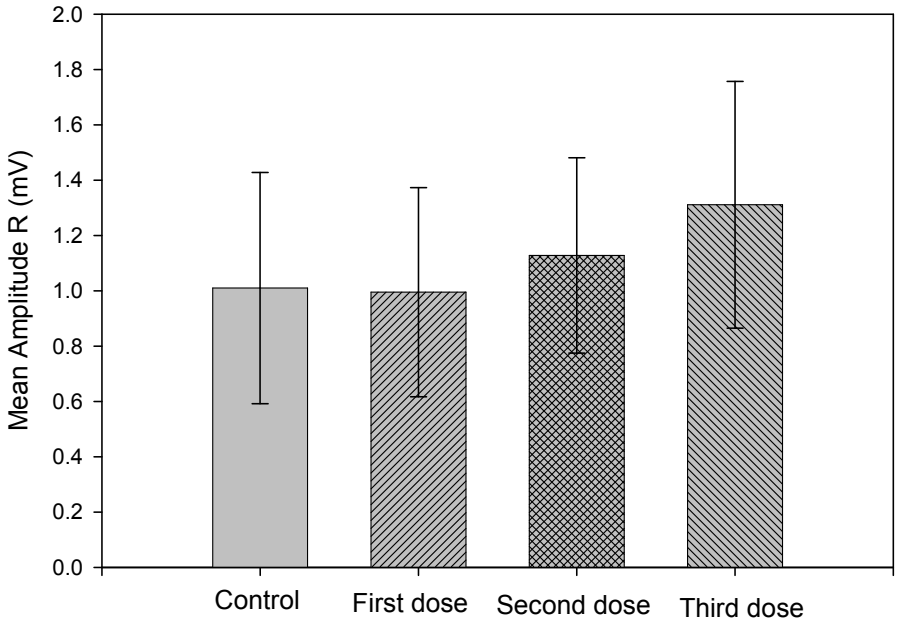

Figure - 6: Effects of carvedilol on R wave amplitude in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9).

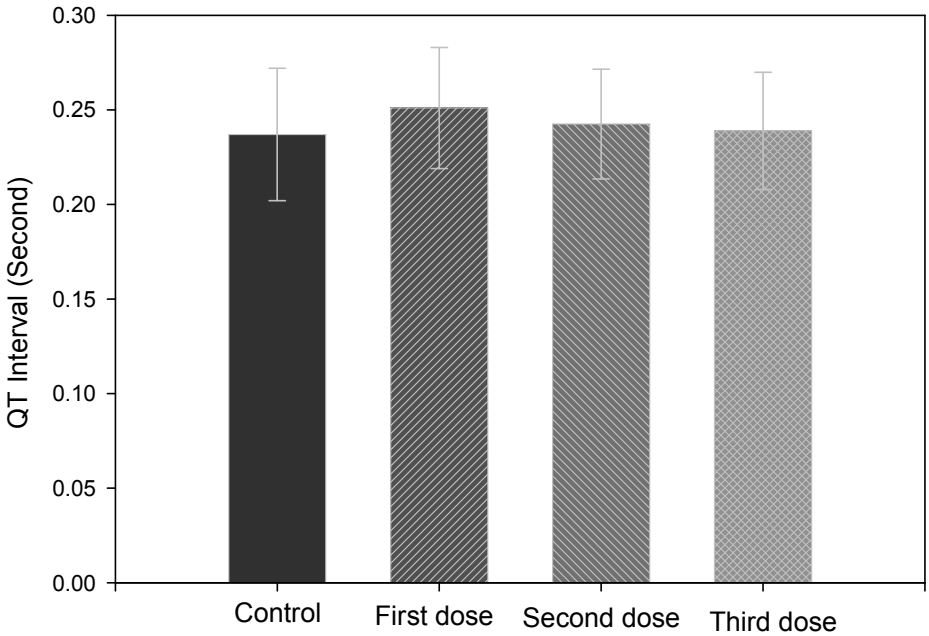

Figure - 7: Effects of carvedilol on Q-T interval in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9).

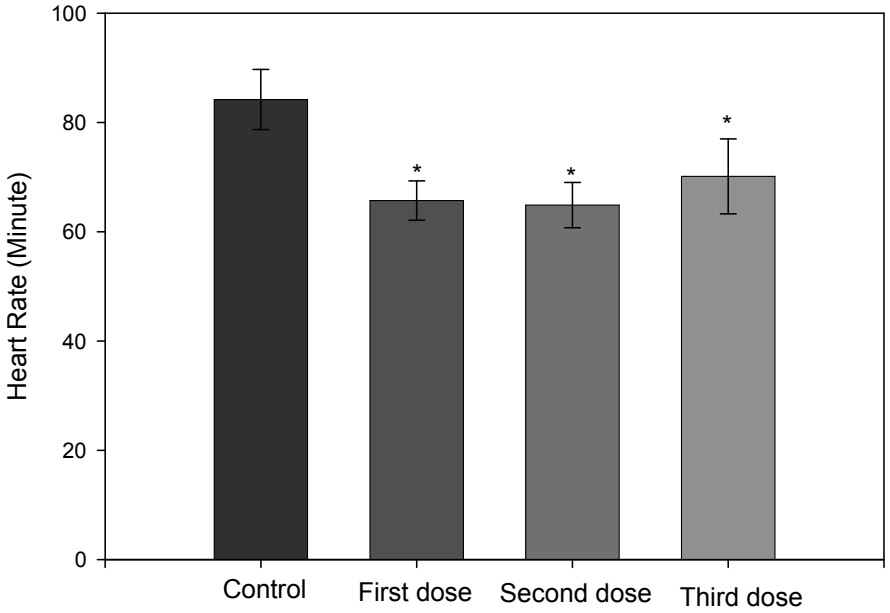

Figure - 8: Effects of carvedilol on heart rate (R-R interval) in control, 0.75 mg.kg^{-1} (First dose), 1.5 mg.kg^{-1} (Second dose) and 3 mg.kg^{-1} (Third dose) groups. Each value represents Mean ± S.D. (n = 9). Asterisks symbol indicate cases with $P < 0.05$ in comparison with the control group.

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