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Furosemide Induced Electrocardiographic Alterations in High Producing Holstein Dairy Cows

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Abstract

Diuretics have several therapeutic advantages in dairy cows but there are different side effects such as acid-base and electrolyte imbalances which may affect the electrocardiographic parameters. Fifteen multiparous, clinically healthy, non-pregnant and high producing 4-year-old Holstein dairy cows at their early lactation period were randomly divided into 3 equal experimental groups. Furosemide was infused intravenously at 3 different doses containing group 1: 2.5 mg/kg; group 2: 5 mg/kg and group 3: 10 mg/kg. Electrocardiogram recordings and blood samplings were performed at prior and 1, 2, 3, 4, 5 and 24 hours after furosemide administrations. Sera after separation were assayed for sodium, potassium, chloride, calcium, magnesium and phosphorus concentrations. There were no significant changing patterns in P, R, S and T amplitudes. P-R, R-R, Q-T and S-T intervals increased significantly after furosemide administrations in groups 2 and 3. Electrocardiographic intervals in groups 3 were higher than other groups (P<0.05). The values of P, R, S and T durations in group 3 increased significantly after furosemide administration. Durations of these waves in group 3 were higher than groups 1 and 2, significantly (P<0.05). There were no significant changing patterns in serum calcium, magnesium and phosphorus levels. Serum concentrations of sodium, potassium and chloride significantly decreased after furosemide administrations in all experimental groups. Levels of these electrolytes in group 3 were significantly lower than other groups (P<0.05). It may be stated that furosemide affects the electrocardiographic parameters by misbalancing the serum electrolytes which affect the electrical conduction of action potential in the myocardium.

Keywords: Furosemide, Electrocardiogram, Electrolyte imbalance, Holstein dairy cow.

Introduction

Measuring and evaluating the heart electrical activities can be performed by the electrocardiogram (ECG) which is a noninvasive and inexpensive diagnostic technique. Some of the cardiac problems can be detected by clinical evaluations such as auscultation but the executive details of cardiac electrical performance should be detected by using ECG (Radostits *et al.* 2007). There are different electrocardiographic leads to record the electrical activities of the heart. Among them, base apex lead has been used for large animals and it is shown to be an appropriate lead; Moreover, ECGs recorded in this lead has clear and large waves and complexes and animal movement has a minimum effect on the recording (Santamarina *et al.* 2001). The majority of arrhythmias and conduction disturbances can be detected on clinical examination (Radostits *et al.* 2007); however, several researchers recorded the cardiac abnormalities of the large animals which have not been detected by clinical investigations (Pourjafar *et al.* 2012a; Chalmeh, 2014; Chalmeh *et al.* 2014).

Several studies reported the normal electrocardiographic parameters in large animals such as cattle (Pourjafar *et al.* 2012a), camel (Pourjafar *et al.* 2011a), sheep and goat (Ahmed and Sanyal, 2008), etc.

Alterations of the heart electrical activities in large animals including physiological (Pourjafar *et al.* 2011b; Pourjafar *et al.* 2012b) and pathological (Austin *et al.* 1997; Mir *et al.* 2007) abnormalities are mentioned. Physiological variations in the cardiac electrical activities in normal animals may be detected electrocardiographically due to autonomic influence, primary myocardial disease and acid-base and electrolyte imbalances (Radostits *et al.* 2007).

Diuretic agents such as furosemide have several therapeutic advantages in dairy cows. These drugs are used to resolve congestive heart failure, pulmonary edema, hepatic and renal diseases, etc. But in addition to the advantages, there are different side effects such as acid-base and electrolyte imbalances (Radostits *et al.* 2007). Due to their effects on circulating electrolyte profile, it can be hypothesized that diuretics may potentially affect the cardiac electrical production and conduction. Since the furosemide has different therapeutic uses in dairy cows, the present experimental study was performed to evaluate the probable alterations of heart electrical activities by ECG recording in clinically healthy multiparous high producing Holstein dairy cows following bolus intravenous furosemide administration at different doses.

Materials and methods

Animals

The current study was conducted in October 2015 on 15 multiparous, clinically healthy and non-pregnant 4-year-old Holstein dairy cows (550±50 kg body weight) in an industrial dairy farm around Shiraz, Fars province, southwest of Iran. These cows were housed in open-shed barns with free access to water and shade. The total mixed rations were formulated and prepared for all animals according to National Research Council (NRC) requirements. At this farm, a dry period of 60 days has been considered. Milk production was about 10,000 kg for year, an average of 3.6% of milk fat, and 3.3% of milk protein. All animals were clinically healthy, had not history of debilitating disease and clinical signs of cardiovascular insufficiencies (edema, jugular distension or pulsation and cardiac murmurs). The body condition score (BCS) of these animals was estimated based on 0 to 5 system. Cattle were in early lactation period (30.2±5.7 days after calving, with 3.25±0.25 BCS).

Experimental design

Animals were randomly divided into 3 equal experimental groups. A 16 gauge, 5.1 cm catheter was secured in the left jugular vein and used for drug infusion and blood samplings. Furosemide (Vetasomide®, Aburaihan Co., Iran) was infused intravenously at 3 different doses containing group 1: 2.5 mg/kg; group 2: 5 mg/kg and group 3: 10 mg/kg. ECG recordings and blood samplings were performed immediately before and 1, 2, 3, 4, 5 and 24 hours after furosemide administrations.

Electrocardiographic studies

The ECGs were recorded on a bipolar base apex lead, using limb lead I. Animals were kept standing without any sedation and minimum restraint. When animals became calm, the ECGs were recorded, using alligator-type electrodes which were attached to skin after cleaning it with ethanol and applying electrocardiographic

jelly to improve skin contact. The positive electrode (left arm) was placed over cardiac apex on the 5th left intercostal space at the level of the elbow, the negative electrode (right arm) was placed on the left jugular furrow at the top of heart base, and the neutral electrode was placed on the dorsal spine or another site away from the heart (Radostits *et al.* 2007). All ECGs were obtained in a single channel electrocardiographic machine (Kenz-line EKG 110, Suzuken Co., Ltd., Japan) with paper speed of 25 mm/sec and calibration of 10 mm/1 mV. The precision of duration was 0.02 s, the amplitude 0.05 mV.

Serum electrolytes profile

Blood samples were collected from all cows through the fixed catheter in plain tubes. Immediately after blood collections, sera were separated by centrifugation (10 min at 3,000×g) and stored at −22 ℃ until assayed. Sera were assayed for sodium, potassium, chloride, calcium, magnesium and phosphorus concentrations. Serum chloride and phosphorus were analyzed using routine biochemical procedures (Burtis and Ashwood, 1994). The serum concentrations of sodium and potassium were measured by the flame photometry (Flame Photometer, FLM, Ontario, Canada). The samples were also analyzed for magnesium and calcium by atomic absorption spectroscopy (Shimadzo AA-670, Japan).

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical analyses were performed using one-way ANOVA with LSD post-hoc test to compare mean concentrations of different electrocardiographic parameters and electrolytes within similar hours among different experimental groups. Repeated measures ANOVA was also used to study the changes in pattern of different electrocardiographic parameters and serum electrolytes in each group, statistically, using SPSS software (SPSS for Windows, version 11.5, SPSS Inc, Chicago, Illinois). The level of significance was set at $P<0.05$.

Results

Effects of intravenous furosemide administrations on electrocardiographic parameters and serum electrolytes profile of high producing Holstein dairy cows are presented in Figures 2 to 6.

As can the seen, there were no significant changing patterns in P, R, S and T amplitudes. These electrocardiographic parameters in an hour of each group were not statistically different from similar hour of the other groups ($P>0.05$; Figure 2). P-R, R-R, Q-T and S-T intervals increased significantly after furosemide administrations in groups 2 and 3. Electrocardiographic intervals in groups 3 were significantly higher than other groups ($P<0.05$; Figure 3). The values of P, R, S and T durations in group 3 increased significantly after furosemide administration. Durations of these waves in group 3 were higher than groups 1 and 2, significantly ($P<0.05$; Figure 4).

There were no significant changing patterns in serum calcium, magnesium and phosphorus levels following furosemide administrations at different doses in dairy cows. The levels of these electrolytes in each group, at similar hours, were not significantly different from the other ones ($P>0.05$; Figure 5). Serum concentrations of sodium, potassium and chloride significantly decreased after furosemide administrations in all experimental

groups. Levels of these electrolytes in group 3 were significantly lower than other groups ($P<0.05$; Figure 6).

Figure 1- *Normal electrocardiogram tracing from an adult multiparous high producing Holstein dairy cow (base apex lead, paper speed 25 mm/sec, sensitivity 10 mm/mV).*

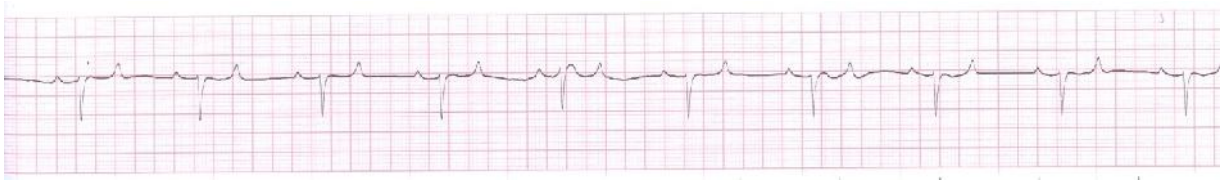


Figure 2- *Effects of intravenous furosemide administration on amplitudes (Mean±SD) of electrocardiographic waves of high producing Holstein dairy cows.*

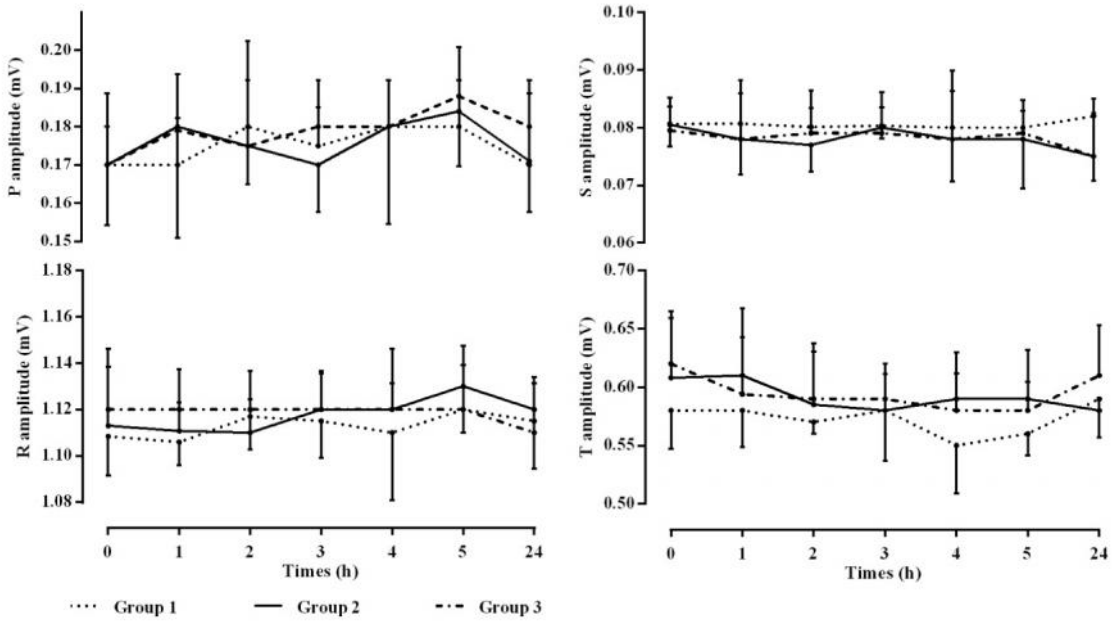


Figure 3- *Effects of intravenous furosemide administration on intervals (Mean±SD) of electrocardiographic waves of high producing Holstein dairy cows. Different letters indicate significant differences in similar hours among groups (P<0.05).*

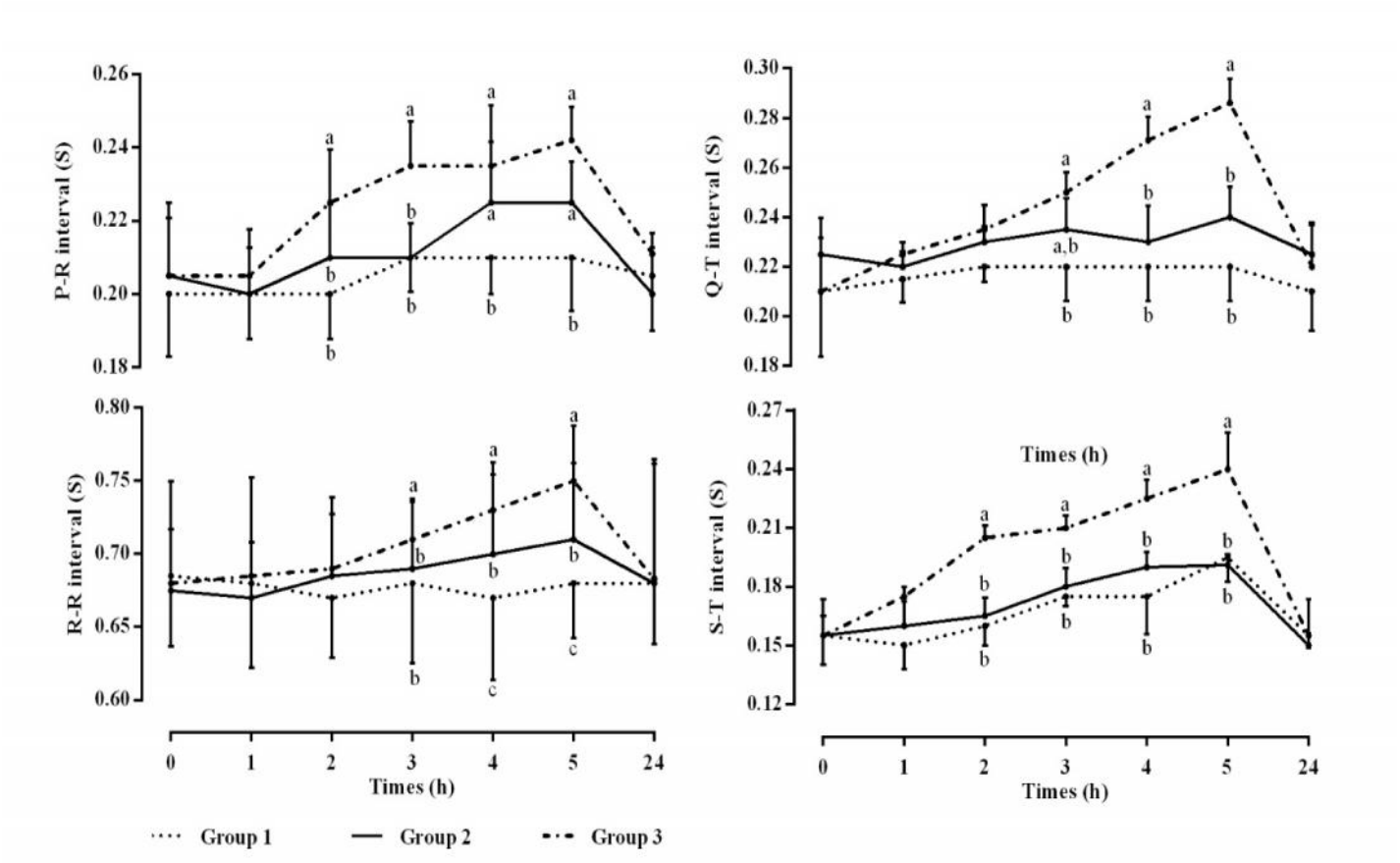


Figure 4- *Effects of intravenous furosemide administration on durations (Mean±SD) of electrocardiographic waves of high producing Holstein dairy cows. Different letters indicate significant differences in similar hours among groups (P<0.05).*

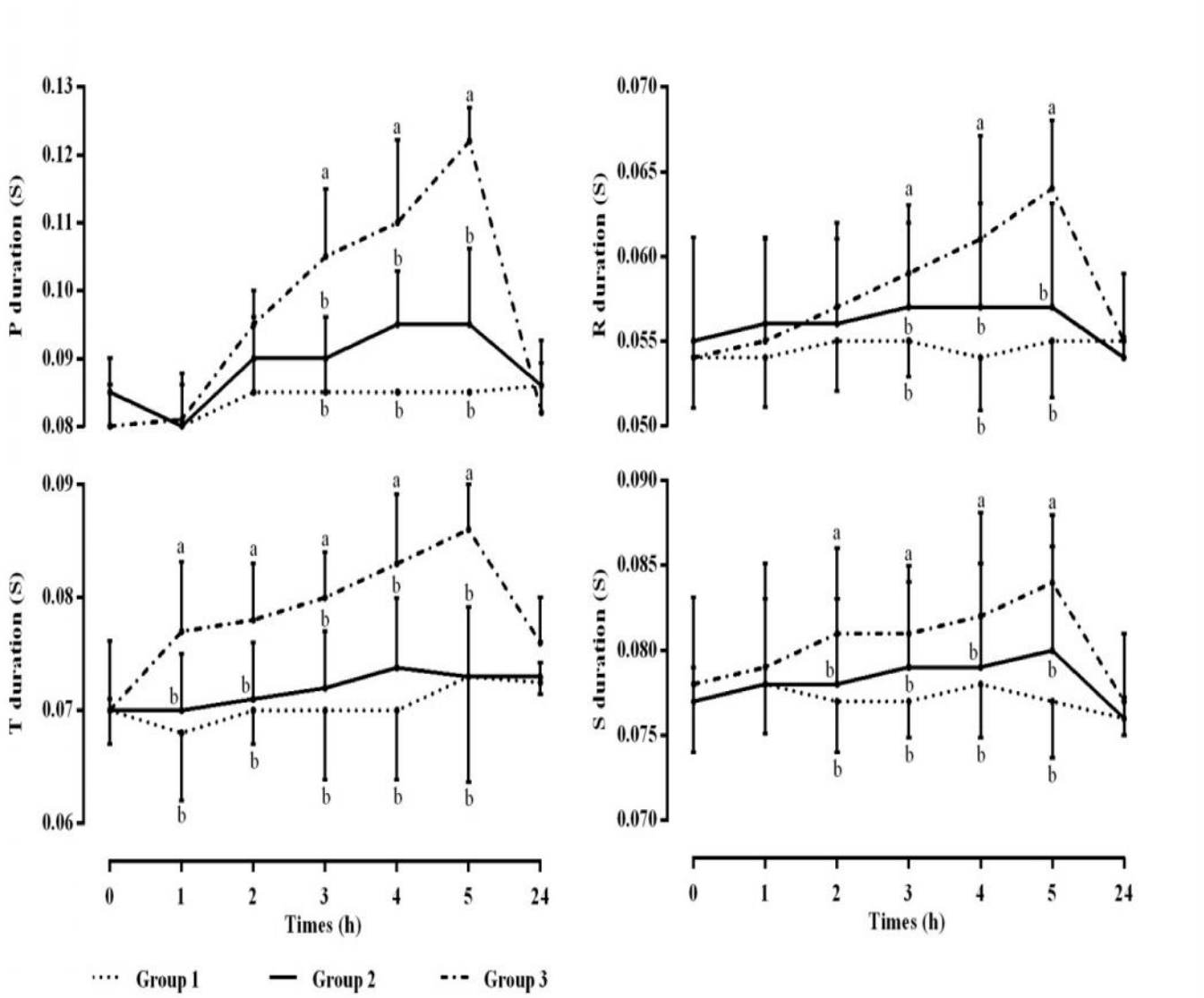


Figure 5*- Effects of intravenous furosemide administration on serum calcium, magnesium and phosphorous (Mean±SD) of high producing Holstein dairy cows.*

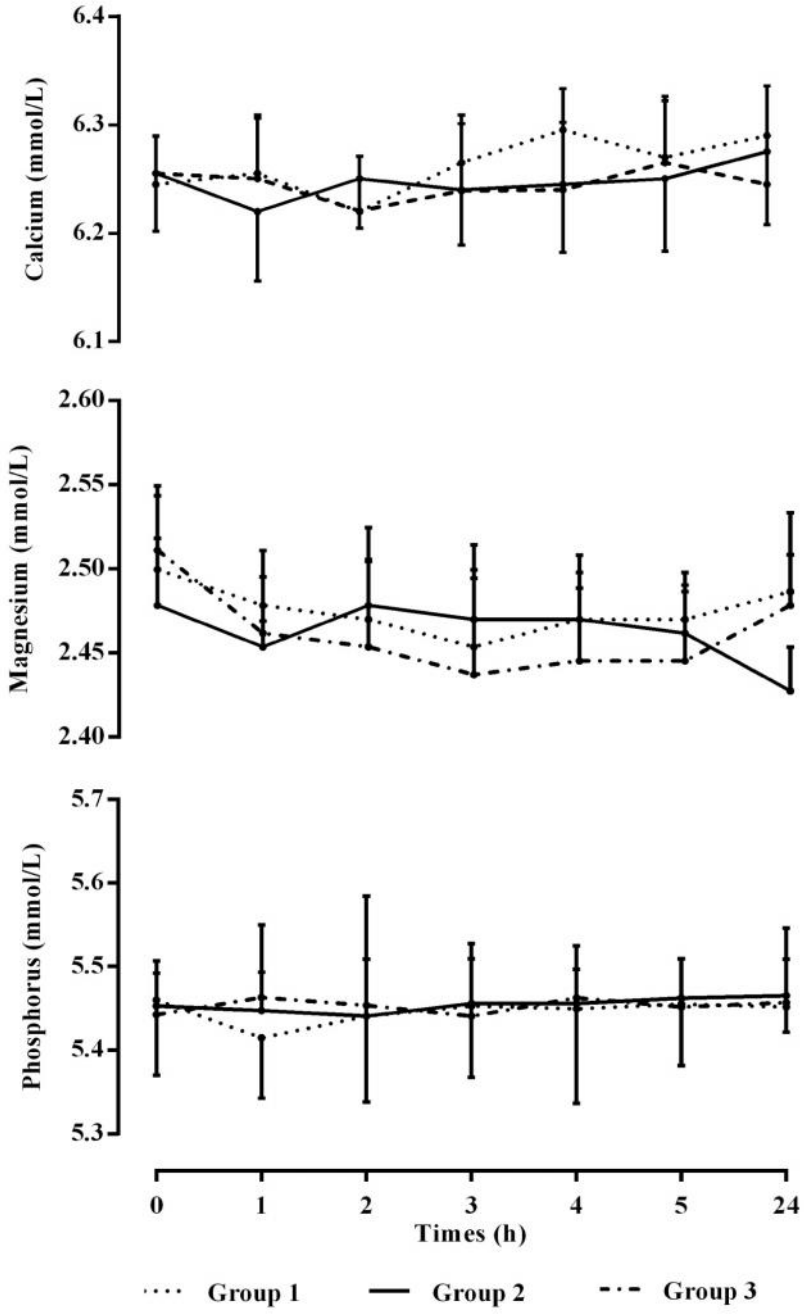
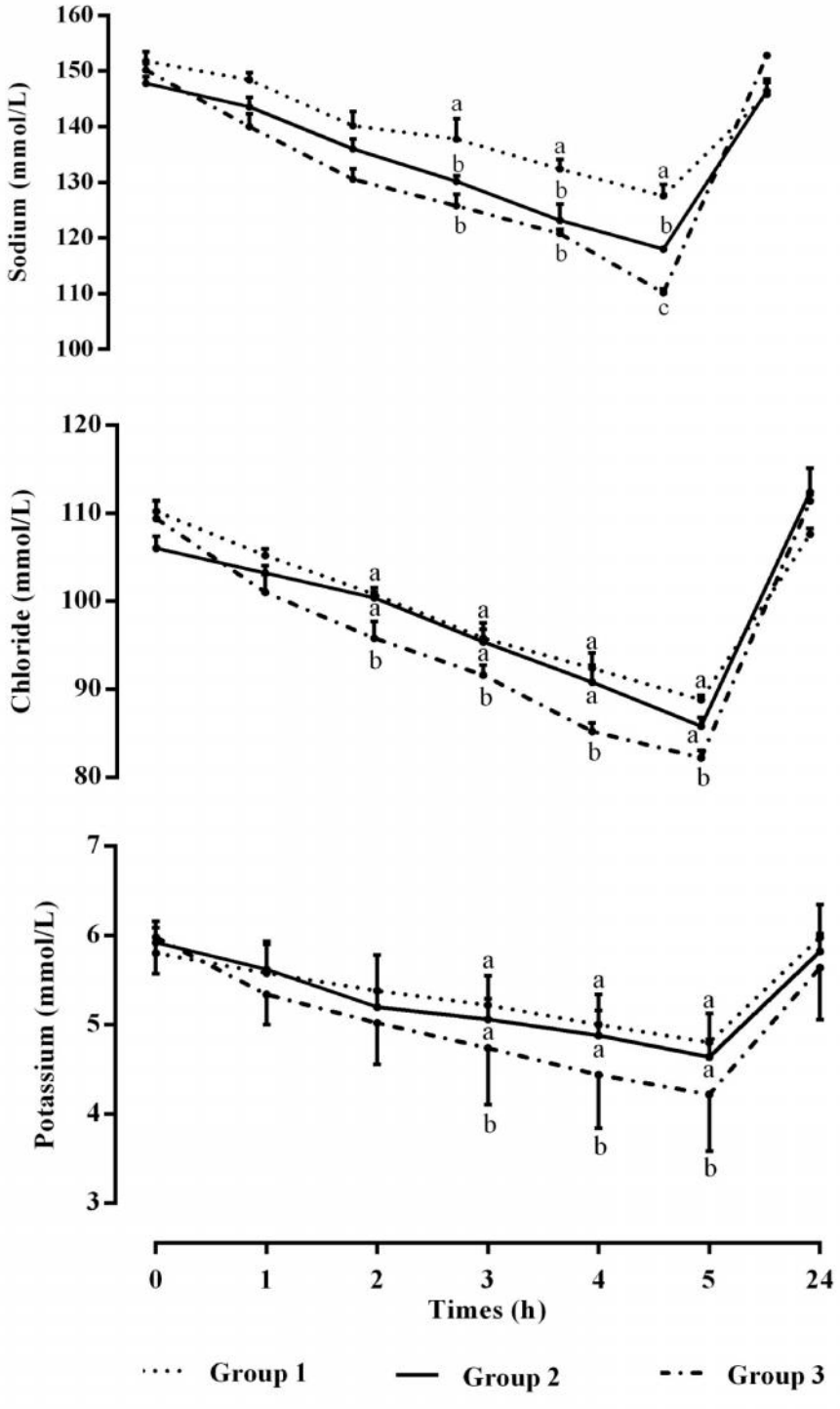


Figure 6*- Effects of intravenous furosemide administration on serum sodium, potassium and chloride (Mean±SD) of high producing Holstein dairy cows. Different letters indicate significant differences in similar hours among groups (P<0.05).*



Discussion

Loop diuretics are agents that affect the ascending loop of Henle in the kidney. These drugs are commonly used to resolve different problems in large animals such as treat hypertension, congestive heart failure, edema and renal insufficiency (Radostits *et al.* 2007). Furosemide is one of the most common loop diuretics in large animal medicine. This drug acts on the sodium, potassium and chloride in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption. This is achieved by competing for the chloride binding site. Reabsorption of magnesium and calcium in the thick ascending limb is dependent on the positive lumen voltage gradient. This is set up by potassium recycling through renal outer medullary potassium channel. Beside the effects of furosemide on the loop of Henle, several side effects can be taking place (Bushinsky *et al.* 1986). The most common adverse drug reactions of furosemide are dose-related due electrolyte imbalance. Common adverse drug reactions include hyponatremia, hypokalemia, hypomagnesemia, dehydration, hyperuricemia, postural hypotension and syncope. This electrolyte imbalance is known as an important factor which affects ECG (Greenberg, 2000; Radostits *et al.* 2007).

Based on the results of the present study, no significant changing patterns were seen in the calcium, magnesium and phosphorous concentrations in each group and also among all experimental groups (P>0.05; Figure 5). Sodium, chloride and potassium concentrations decreased after furosemide administrations in all groups. The lowest concentrations of these electrolytes were detected at 5^{th} hour after drug administrations. The concentrations of sodium, chloride and potassium in group 3 were significantly lower than other groups (P<0.05; Figure 6).

Due to the distribution of the main intra and extracellular electrolytes such as sodium, potassium and chloride, the interior of cardiac cells is negative. In myocardial cells, the interior is maintained more negative than the exterior by the extrusion of 3 sodium ions for every 2 potassium ions pumped in by the sodium/potassium ATPase pump. Movement of electrolytes across the impermeable cell membrane is through a number of channels (sodium and potassium channels, e.g.) that permit or prevent the movement of ions depending upon transmembrane voltage. Whereas calcium is the main electrolyte responsible for pacemaker cell depolarization, sodium is the main electrolyte responsible for depolarization of myocardial cells and cells dedicated to conduction of impulses (Fisch, 1984).

In humans, hypokalaemia is known to produce typical changes in the T wave, in particular decreased amplitude and the appearance of a U wave (Surawicz *et al.* 1957). Similar changes have been observed in hypokalaemic dogs (Felkai, 1985). In Hanton *et al.*'s study (2007), hypokalaemia was also associated with decreasing amplitude of the T wave and with morphological changes in tracings recorded in CV5RL. The results of the present study showed that there were no significant changing patterns in all amplitudes. Furthermore, there were no significant differences among the amplitudes of all experimental groups (P>0.05; Figure 2).

Rapid repolarization of the ventricular cells takes place via the potassium exchanges from cardiac cell

membranes (Gadsby *et al.* 1995). Hypokalaemia increases the duration of cardiac action potential and, consequently, prolongs QT interval. The inhibition of cardiac repolarization associated with a decrease in extracellular potassium is assumed to be related to faster inactivation of potassium channels responsible for delayed potassium outflow and consequent inhibition of repolarization currents (Yang *et al.* 1997). The P-R interval can be prolonged along with an increase in the amplitude of the P wave (Drighil *et al.* 2007). In the present study, the P-R, R-R, Q-T and S-T intervals increased significantly in groups 2 and 3. The levels of these parameters in group 3 were significantly higher than other groups ($P<0.05$; Figure 3).

Akita *et al.* (1998) demonstrated that the ECG changes induced by hypokalemia in the rat occurred and there were included Q-T interval prolongation and decreasing the amplitude of all waves except P waves. A prolonged Q-T interval is also a typical ECG manifestation of hypokalemia. A low extracellular potassium concentration produced a prolonged action potential and increased the time of diastolic depolarization (Gettes and Surawitz, 1968).

In humans, the cardiac effect of hypokalaemia is well documented. Decreases in potassium plasma levels may occur in different pathological states and may be produced by a number of drugs (Cohen *et al.* 2002). Hypokalaemia may have a major effect on cardiac repolarization and ECG durations (Yelamanchi *et al.* 2001).

Hyponatraemia would have a Q-T prolongation effect similar to that of hypokalaemia (Yelamanchi *et al.* 2001). However, sodium produces electrophysiogical abnormalities only at concentrations higher than physiological range (Surawicz, 1995). Theoretically, reduction of the extra cellular concentration of sodium should slow cardiac pacemaker activity. In animal models, wide QRS complexes, either through hyperkalemia or quinidine administration, have been documented (Surawicz, 1995). Hyponatremia plays a role in the pathogenesis of the cardiac conduction defect.

The durations of P, R, S and T waves in group 3 increased significantly after furosemide administration. These electrocardiographic parameters in group 3 were significantly higher than other groups ($P<0.05$; Figure 4). An increase in durations occurred simultaneously with the decrease in plasma potassium level following the effect of a potent diuretic. A number of publications report high values of durations in dogs with severe hypokalaemia (Weissenburger *et al.* 1991).

In conclusion, the results of the present study showed that administrating the furosemide as a common diuretic in large animals can affect the electrocardiographic parameters. Furthermore, the effects of this agent are dose related, therefore, the higher doses induce more electrocardiographic alterations. Based on the results; it may be stated that furosemide affects the ECG parameters by misbalancing the serum acid-base and electrolytes after its intravenous administration in high producing Holstein dairy cows. These electrolyte imbalances can affect the electrical conduction of action potential in the myocardium and ECG, subsequently. Hence, electrocardiographic alterations can be considered as furosemide side effects in a dose dependent manner.

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تاثیر فوروزماید بر تغییرات الکتروکاردیوگرافیک در گاوهای هلشتاین شیری پرتولید

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چکیده:

داروهای ادرارآور مزایای درمانی فراوانی در گاوهای شیری دارند، اما در کنار این مزایا دارای اثرات جانبی نیز می باشند که شامل تغییر در توازن الکترولیتی و اسید-باز بدن است، که این تغییرات باعث اثر بر پارامترهای خونی که روی سیستم قلب و عروق موثرند، می شوند. در همین راستا ۱۵ رأس گاو هلشتاین ٤ ساله غیر آبستن به ظاهر سالم و پر تولید که در مرحله ابتدای شیردهی بودند انتخاب شده و به صورت تصادفی در ۳ گروه تجربی دسته بندی شدند. سپس تزریق داخل وریدی فوروزماید در سه دز مختلف به هر کدام از گروه ها صورت گرفت: گروه ۱: ۲/۵ میلی گرم/کیلوگرم، گروه ۲: ۵ میلی گرم/کیلوگرم و گروه۳: ۱۰ میلی گرم/کیلوگرم. از تمام گاوها الکتروکاردیوگرام اخذ و در زمان های ۱، ۲، ۳، ٤، ۵ و ۲٤ ساعت پس از تزریق فوروزماید خونگیری به عمل آمد و سپس مقادیر سدیم، پتاسیم، کلراید، کلسیم، منیزیم و فسفر در سرم های جدا شده ارزیابی شد. در همین راستا هیچ تغییر معنی داری در دامنه امواج P، R، S و T دیده نشد، پس از تزریق فوروزماید در گروه ۲ و ۳ افزایش معنی داری در فواصل P-R، R-R، Q-T و S-T دیده شد، همچنین فواصل الکتروکاردیوگرافیک در گروه ۳ به طور معنی داری از سایر گروه ها بیشتر بود (P<۰/۰۵). پس از تزریق فوروزماید، طول امواج P، R، S و T در گروه ۳ به طور معنی داری افزایش پیدا کرد، همچنین به طور معنی داری مدت زمان این امواج در گروه ۳ نسبت به گروه ۱ و ۲ افزایش یافت (P<۰/۰۵). در تمام گروه های مورد مطالعه، پس از تزریق فوروزماید، تغییرات معنی داری در میزان کلسیم، منیزیم و فسفر سرم دیده نشد، در صورتی که میزان سدیم، پتاسیم و کلراید سرم به طور معنی داری کاهش یافت. سطح الکترولیت ها در گروه ۳ به طور معنی داری کمتر از دیگر گروه ها بود (P<۰/۰۵). در نهایت اینگونه برآورد می شود که فوروزماید بر امواج الکتروکاردیوگرافیک موثر است و این تاثیر به سبب اختلالات الکترولیتی بدن و با اثر بر سیستم هدایت جریان الکتریکی بر پتانسیل عمل میوکاردیوم است.

واژه‌گان کلیدی: فوروزماید، الکتروکاردیوگرام، عدم تعادل الکترولیت ها، گاو شیری هلشتاین