Global Veterinaria 9 (3): 277-283, 2012
ISSN 1992-6197

DOI: 10.5829/idosi.gv.2012.9.3.65102

Effects of Halothane Anesthesia on ECG and Some Physiological Parameters in Unilateral Nephrectomized Dogs

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Abstract: The purpose of the present study was to evaluate effects of halothane anesthesia on ECG and some physiological parameters in unilateral nephrectomized dogs which was conducted on 10 male dogs with an average weight of 23.18±4.7 Kg and 2 years of age. 14 days following the nephrectomy, inhalation anesthesia was induced by halothane for 180 minutes. Heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure, mean blood pressure and SPO_2 were recorded at time 0 (before anesthesia induction) and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180 minutes after onset of anesthesia. Normal ECG parameters were recorded before the beginning of the experiment, at induction time and at 0, 10, 20, 30, 60, 90, 120, 150, 180, 210 minutes after anesthesia initiation. Heart rate, ECG pattern, amplitude and configuration, segments and intervals were measured and compared between basal level (after nephrectomy and before anesthesia induction) and after halothane anesthesia. Results showed that respiratory rate significantly increased at 105 minutes after onset of anesthesia in comparison with the beginning of the experiment, while SPO_2 significantly reduced at 60, 90, 105, 120, 135, 150 and 165 minutes after onset of anesthesia ($P<0.05$). The amplitude of P wave and QRS complex significantly decreased at 60 minutes after onset of anesthesia. Prolongation of QT interval occurred at 90 and 150 minutes after onset of anesthesia in comparison with time 0. ST segment significantly prolonged during anesthesia in comparison with time 0 ($P<0.05$). Respiratory sinus arrhythmia was recognized in 7 cases previous to the beginning of the experiment. However, halothane anesthesia did not significantly affect them, except for 4 cases at induction time and 1 case at the time 0. Respiratory sinus arrhythmia reappeared in 2 cases at 20 minutes after onset of anesthesia. The occurrence of first degree AV block (1 case), sinoatrial block (1 case) and brady cardia (1 case) was recorded at 10 minutes after onset of anesthesia. Ultimately, it was concluded from the results that unilateral nephrectomized dogs could restore their circulatory system during halothane anesthesia, without any complication.

Key words: Halothane · Dog · Anesthesia · ECG · Nephrectomy

INTRODUCTION

Various agents contribute to cause arrhythmia during anesthesia and surgery. Changes in sympathetic activity and vagotonic action, electrolytes and Acid-Base balance distribution are considered as the most important factors. Tracheal intubation, manipulations during the surgery and cardiovascular diseases also impact on frequency of arrhythmias during the anesthesia. Despite common occurrence of arrhythmias during anesthesia and surgery, they don't usually have clinical symptoms [1]. Electrocardiographic alterations in halothane anesthesia were brought to QT interval elongation which makes halothane potent arrhythmogenic agent (Simeonora). Halothane has been reported to cause prolongation of the QT interval. The risk of arrhythmias during halothane anesthesia might increase in certain procedures, clinical states and in some other susceptible populations [2].

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On the other hand, the model, which has evolved as one that produces arguably the most information on the pathophysiology of arrhythmia production, includes the role of the autonomic nervous system and the interaction with pharmacological agents [3]. Wickstrom and Stefansson (1981) reported that significant difference in BUN and Creatinin could be a result of repeated halothane anesthesia in long duration time which leads to renal injuries, reduction of glomerular filtration rate and increase in BUN and Creatinin [4]. Kharasch *et al.* showed that renal deficiency following the halothane anesthesia resulted from increase in fluride ion [5]. Increase in BUN and serum Creatinin after halothane anesthesia in comparison with before anesthesia and before and after nephrectomy was proved by Sharifi *et al.* [6]. Degenerative effects of halothane on liver, kidney and brain have been reported, although potential toxicity of halothane on biological systems needs more studies [7]. In the present study, effects of a three-hour halothane anesthesia on blood circulatory system were investigated in 10 male nephrectomized dogs and alterations in heart rate, respiratory rate, boy temperature, systolic and diastolic blood pressure, mean blood pressure, SPO_2andECG parameters were recorded and evaluated.

MATERIAL AND METHODS

Ten male dogs with an average weight of 23.18±4.7 Kg and an average age of 2 year were used. Their state of health was checked based on the range of the heart rate, respiratory rate, rectal body temperature and CBC. Two weeks before the beginning of the experiment, in order to comply with the new environment, animals were transferred to the specialized place for small animal care. Mebendazole at 20 mg/kg and praziquantel at 5 mg/kg were prescribed orally which both were repeated after 15 days. Dogs were prohibited from eating and drinking for 18 hours previous to nephrectomy and a catheter was applied into the left cephalic vein for subsequent fluid administration. Anesthesia was induced by means of a xylazine-ketamine combination at 1 and 5 mg/kg BW respectively. Dogs were connected to a rebreathing system after intubation and a medium plane of anesthesia was maintained by halothane during the surgery. Left unilateral nephrectomy was done in all of the animals. Surgical approach which was taken to nephrectomize dogs is explained by sharifi *et al.* [6]. 14 days following the nephrectomy, in order for anesthesia induction, halothane in 100% oxygen (4 L min^{-1}) was delivered via a fitted face mask. The concentration of halothane was gradually increased (0/5% every 30 sec) until a 4% vaporizer setting was obtained. A medium plane of anesthesia, as determined by palpebral and pedal reflexes, was maintained by halothane (1-1/2%) in oxygen (1/5 L min^{-1}) for 3 hours. The dogs were placed in right lateral recumbency on a padded surgical table during anesthesia. Heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure, mean blood pressure and SPO_2 were assessed at time 0 (before anesthesia induction) and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180 minutes after anesthesia initiation. Electrocardiograms were recorded by Suzukenco model 110 ECG machine (made in Japan) before applying any medication, at induction time, time 0 (anesthesia initiation) and at 10, 20, 30, 60, 90, 120, 150, 180, 210 minutes after onset of anesthesia. Recorded physiological parameters and electrocardiograms were analyzed by One Way Analysis of Variance (ANOVA) tests. Tukey test and Dunnett's method and Pearson correlation were also used for further evaluations. Significance was set at P <0/05.

Induction time (time from administration of halothane to tracheal intubation), extubation time (time from discontinuation of halothane to swallowing reflex) and time to sternal recumbency (time from discontinuation of halothane to sternal recumbency) were recorded during anesthetic induction and recovery.

RESULTS AND DISCUSSION

As it is detectable in Table 1, there is an increase in heart rate from the beginning of the experiment to 120 minutes after onset of anesthesia; however it is not significant. Significant increase in respiratory rate is noticeable at 105 minutes after onset of anesthesia in comparison with the beginning of the experiment ((P=0.048)). There was a significant reduction in SPO_2 at 60, 90, 105, 120, 135, 150, 165 minutes after onset of anesthesia in comparison with the beginning of the experiment (P<0.05). This reduction was also observed at 105 minutes in comparison with 30 (P=0.019) and 45 (P=0.008) minutes following the initiation of anesthesia. Pearson correlation test results indicated that there was a significant negative correlation with correlation coefficient equal to -0.724 between heart rate and diastolic blood pressure at 15 minutes after onset of anesthesia. In other words, increase in heart rate

Table 1: Changes in parameters related to circulatory system in nephrectomized dogs after halothane anesthesia induction

	0	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	135 min	150 min	165 min	180 min
Heart rate	91/2 ± 8/66	92/10 ± 9/78	91/30 ± 7/13	92/30 ± 6/47	93/70 ± 6/68	92/90 ± 5/93	97/30 ± 6/00	96/70 ± 5/83	98/70 ± 5/89	101/4 ±5/99	100/6 ± 6/38	101/6 ± 6/19	102/8 ± 6/31
Respiratory rate	15/7 ± 3/3	16/80 ± 3/82	18/00 ± 3/83	19/50 ± 4/39	18/20 ± 1/87	18/90 ± 2/08	19/20 ± 2/833	20/80* ± 2/53	19/20 ± 2/71	22/20 ±4/13	21/60 ± 4/70	21/60 ± 4/70	22/8 ± 4/86
Systolic pressure	94/24 ± 4/42	95/20 ± 2/89	96/10 ± 3/15	97/30 ± 6/01	99/80 ± 6/18	101/9 ± 5/91	102± 5/98	103/7 ± 4/88	97/70 ± 3/65	97/60 ±2/52	96/80 ± 3/87	94/90 ± 3/99	94/1 ± 3/78
Diastolic pressure	44/54 ± 3/45	42/00 ± 3/59	52/50 ± 4/37	51/80 ± 7/92	51/60 ± 8/91	55/40 ± 8/35	51/70 ± 9/13	50± 5/61	47/10 ± 4/3	48 ±30/7	42/60 ± 4/76	50/10 ± 4/17	46/45 ± 4/23
Mean blood pressure	65/78 ± 6/87	67/90 ± 3/31	70/20 ± 3/91	73/70 ± 6/97	79/40 ± 6/61	76/70 ± 6/99	74/80 ± 8/05	74/70 ± 6/37	73/20 ± 2/92	71/60 ± 2/61	65/40 ± 5/81	70/40 ± 3/36	70/10 ± 3/37
Tem perature	37/34 ± 1/23	38/23 ± 3/19	38/15 ± 0/20	38/06 ± 0/22	37/99 ± 0/21	38 ± 0/22	37/84 ± 0/25	37/91 ± 0/27	37/77 ± 0/27	37/74 ± 0/28	37/73 ± 0/31	37/68 ± 0/31	37/66 ± 0/31
SPO_2	98/7 ± 0/46	98 ± 0/28	97/44 ± 0/33	97/66 ± 0/33	96/55 * ± 0/53	96/88 ± 0/48	96/66* ± 0/50	96* ± 0/44	96/77* ± 0/54	96/77* ± 0/54	96/77* ± 0/46	96/88* ±0/56	97/11* ± 0/48

Table 2: Frequency distribution of arrhythmias and changes in ECG parameters in nephrectomized dogs after halothane anesthesia induction

Time	Respiratory sinus arrhythmia	Tachy cardia	Brady cardia	Wandering pacemaker	Sinoatrial block	1[th]degree A-V block	ST slure	T wave shape +	T wave shape -	T wave shape biphasic
Before induction	7	-	-	1	-	-	-	8	2	-
Induction time	3	2	1	-	-	-	-	6	1	3
0	2	-	-	-	-	-	-	6	3	1
10 min	2	-	1	-	1	1	-	4	4	2
20 min	4	-	1	-	-	-	-	6	3	1
30 min	2	-	-	-	-	-	-	6	3	1
60 min	2	-	-	-	-	-	-	6	3	1
90 min	2	-	-	1	-	-	1	6	3	1

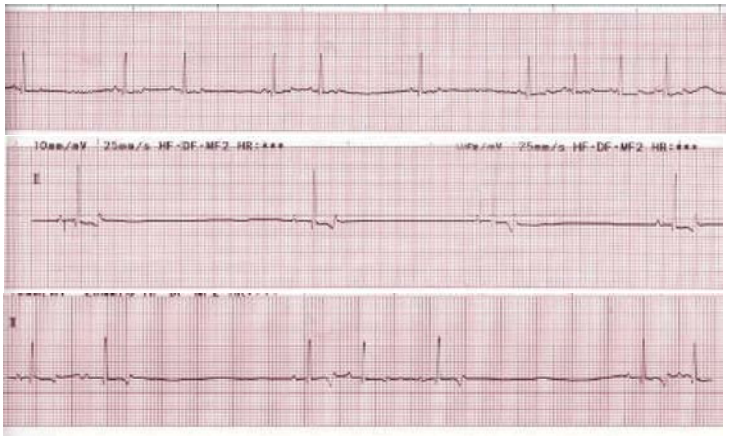

Fig. 1: Presence of respiratory sinus arrhythmia before anesthesia induction (1[th]), Brady cardia occurrence at halothane induction time (2[th]), Reappearance of respiratory sinus arrhythmia associated with biphasic T wave at 150 min after onset of anesthesia (3[th]).

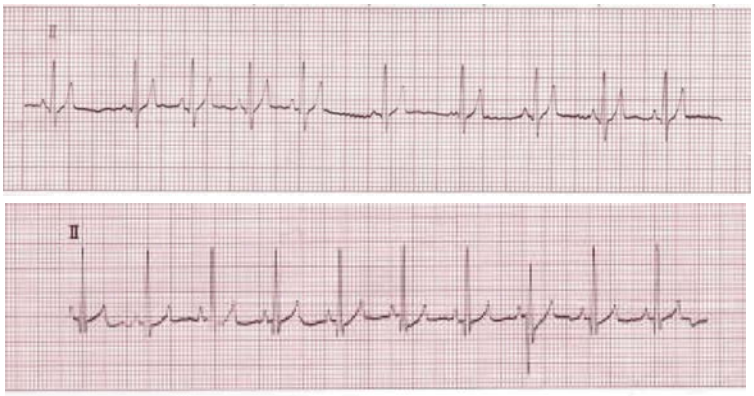

Fig. 2: Presence of respiratory sinus arrhythmia associated with wandering pacemaker before anesthesia induction (1[th]), Occurrence of ST Slure associated with an increase in amplitude of QRS complex at 90 min after onset of anesthesia (2[th]).

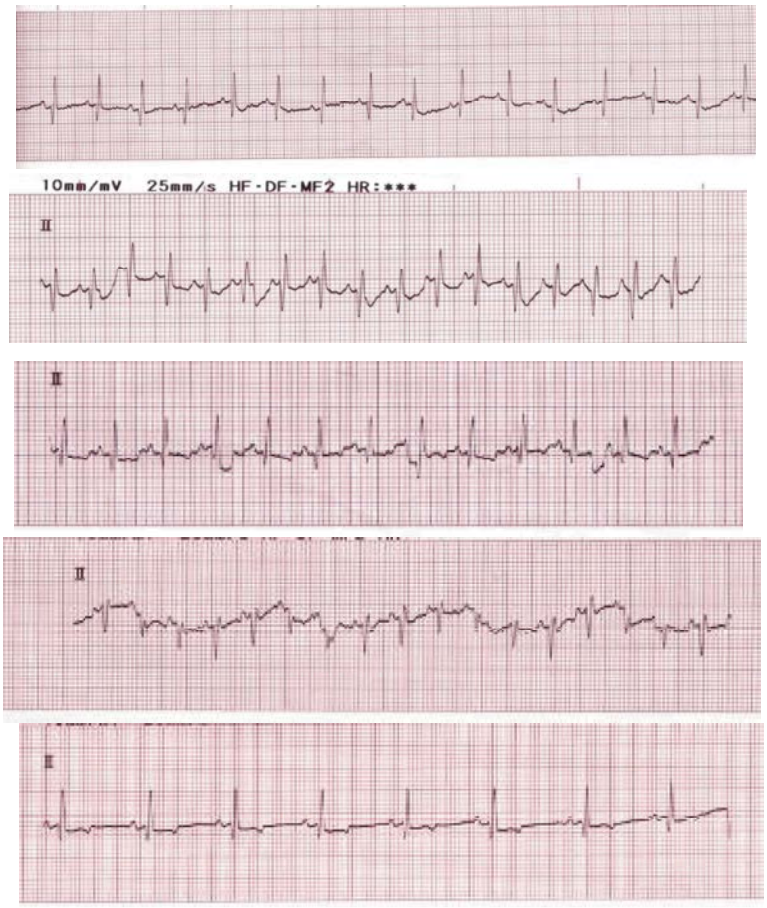

Fig. 3: Normal heart rate previous to halothane anesthesia induction (1th), Tachy cardia occurrence at halothane induction time (2th), Appearance of negative T wave associated with occurrence of trigeminy at time 0 (3),th Negative QRS complex at 10 min after onset of anesthesia (4th), Normal heart rate associated with negative T wave at 20 min after onset of anesthesia (5th).

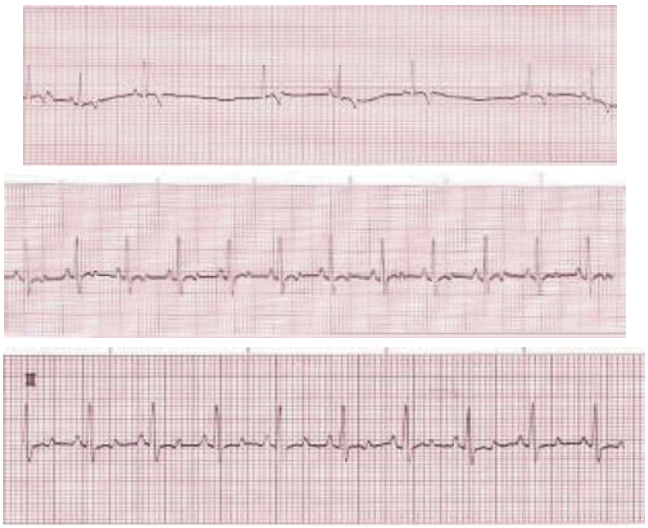

Fig. 4: Respiratory sinus arrhythmia presence associated with negative T wave before anesthesia induction (1th), Normal heart rate and biphasic T wave at anesthesia induction time (2th), Presence of positive T wave at the beginning of the anesthesia (3th).

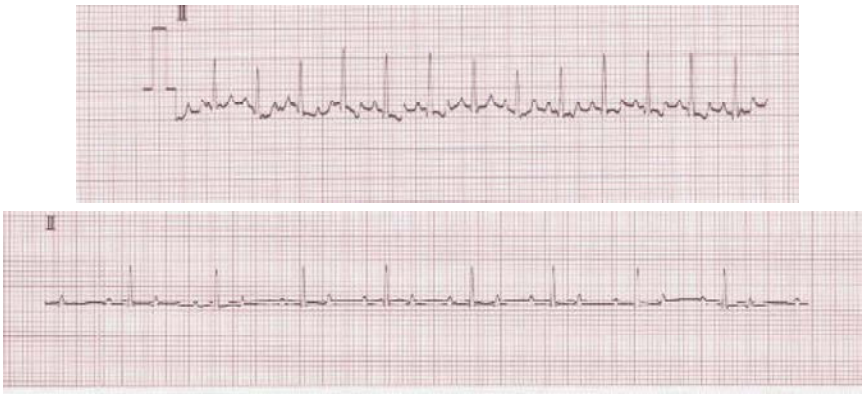

Fig. 5: Occurrence of biphasic T wave at anesthesia induction time (1th), Appearance of first degree AV block at 10 min after onset of anesthesia (2th).

was associated with diastolic blood pressure reduction (P=0.000304). Time enough after anesthesia induction, there was a steady and positive correlation between systolic and diastolic blood pressure at 30, 45, 60, 75, 90, 135, 150 and 180 minutes after onset of anesthesia with correlation coefficient equal to +0.906, +0.959, +0.97, +0.889, +0.827, +0.643, +0.826 and +0.791 respectively (P<0.05). Alteration in electrocardiographic parameters showed that there was a significant reduction in amplitude of P wave (P=0/045) and QRS complex (P=0/048) at 60 minutes after onset of anesthesia in comparison with anesthesia initiation. On the other hand, there was a significant increase in QT interval from time 0 to 90 (P=0/025) and 150 (P=0/039) minutes after onset of anesthesia. During the experiment, there was a significant elevation of ST segment at 20, 30, 60, 90 and120 minutes after onset of anesthesia in comparison with anesthesia initiation with P values equal to 0/029, 0/015, 0/031, 0/005 and 0/032 respectively. The presence of respiratory sinus arrhythmia was recognized in 7 cases before anesthesia induction which disappeared at induction time and at time 0 in 4 and 1 cases respectively and reappeared in 2 cases at 20 minutes after onset of anesthesia. As it is depicted in Table 1 and Figures 1 to 5, the frequency of arrhythmias such as wandering pacemaker, sinoatrial block, first degree AV block and ST slure were 2, 1, 1, 1 cases respectively during the experiment. There were noticeable changes in T wave shape during the experiment. The most frequency of negative T waves was 4 cases at 10 minutes after onset of anesthesia which were associated with increase in biphasic T waves and reduction in positive T waves frequency in comparison with time 0. It is worth mentioning that changes of ECG parameters in Table 2 were reported until 90 minutes after onset of anesthesia, since there were not any notable changes after this time.

Side effects of halothane and increase in renal injuries in long-lasting inhalation anesthesia by halothane were investigated in previous studies [4, 6-7]. Sharifi *et al.* reported that histopathological results on remaining kidney in unilateral nephrectomized dogs showed necrosis in the urinary tubules, hyperemia in glomerulus and cell degeneration. Significant increase was also recorded in BUN and Creatinin at postanesthesia stage in comparison with preanesthesia, prenephrectomy and postnephrectomy stages [6]. The purpose of the present study was to evaluate halothane anesthesia influences on ECG and some physiological parameters in male nephrectomized dogs. The results suggested that nephrectomized dogs managed to balance blood circulatory system and utilization of this pattern in this case and similar cases is acceptable for limited time. As it is detectable in Table 1, there is an increase in respiratory rate from 105 minutes after onset of anesthesia which occurs in response to hypoxia and reduction in SPO_2. There is a significant negative correlation between heart rate and diastolic blood pressure at 15 minutes after onset of anesthesia. In other words, decrease in diastolic duration time (because of tachycardia) results in decrease in diastolic volume and pressure. Nevertheless, it does not persist with the passage of time after anesthesia which indicates cardiovascular favorable performance. The presence of significant positive correlation between systolic and diastolic blood pressure from 30 min after onset of anesthesia evidences optimal response of cardiovascular and respiratory systems to hypoxia. Zucchelli *et al.* investigated side effects of nephrectomy and the process of glomeruloscierosis formation in human which was concerned with increase in glomerular filtration rate as the main factor responsible. In addition, hypertension and thrombotic mechanisms appeared to be

detrimental to glomerulus but seem not to be the initiating agent [8]. However, there is no evidence for sever alteration of blood pressure in nephrectomized dogs in the present study. Takahara *et al.* reported that heart rate, mean blood pressure, maximum upstroke velocity of the left ventricular pressure and cardiac output in contrast to left ventricular end-diastolic pressure were significantly lower in anesthesia induced by halothane in comparison with pentobarbital. Differences in basal cardiohemodynamic variables between the anesthetics may be associated with cellular mechanisms during anesthesia [9]. It was illustrated in previous *in vitro* studies that the anesthetic concentration of halothane decreases the sensitivity of the myofilament to Ca^{2+}, intracellular Ca^{2+} movements and Ca^{2+} currents in both vascular smooth muscle cells and ventricular myocytes [10]. As it is noticeable in Table 2, respiratory sinus arrhythmia was recorded in 7 cases before halothane anesthesia which only remained in 2 cases after anesthesia induction. In Halliwill and Billman's study, the amplitude of the respiratory sinus arrhythmia was determined by heart period (R-R interval) analysis which showed significant decrease in respiratory sinus arrhythmia due to decrease in vagal tone during halothane anesthesia. These data suggested decrease in respiratory sinus arrhythmias as an indicator for vagal activity [11]. Heart rate increases during inhalation anesthesia with substance-specific differences, in spite of the fact that the majority of inhalation anesthetics inhibit sympathetic drive. Picker *et al.* reported that in equianesthtic concentrations, increase in heart rate for desflurane was much more than halothane. Differences in the degree of increase in heart rate might be related to differences in anesthetics' vagolitic action, so that, halothane is considered as an anesthetic with less vagolitic action than other anesthesia agents [12]. Disappearance of wandering pacemaker is also related to vagolitic effects of halothane, although it's recurrence in 1 case at 90 minutes after onset of anesthesia is because of dose dependent depression in SA node triggered by halothane which could lead to reduction in self-stimulation in SA node and initiation of impulses in other pacemaker sites existed in heart [13]. Halothane sensitizes myocard to cathecolamines and in case of epinephrine administration, it causes sever ventricular arrhythmias [14]. On the other hand, increase in inhalation halothane concentration converts ventricular arrhythmia to sinus rhythm [15]. The present study results indicated that QT interval and ST segment prolonged during halothane anesthesia, as it was reported in previous studies [16-17].

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