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SHORT COMMUNICATION

The effects of anesthetic drug choice on heart rate variability in dogs

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ABSTRACT

Objective: The objective of this study was to assess the effects of anesthetic drugs on heart rate (HR) and heart rate variability (HRV) in dogs.
Materials and Methods: Twelve healthy client-owned dogs of various breeds, including five females and seven males were used for elective surgery in this study. The dogs were pre-medicated with four protocols; (1) alfaxalone [at 3 mg/kg body weight (bwt)], (2) zolazepam + tiletamine (Zoletil) (at 5 mg/kg bwt), (3) diazepam (at 0.3 mg/kg bwt) + ketamine (at 5 mg/kg bwt), and (4) diazepam (at 0.3 mg/kg bwt) + propofol (at 5 mg/kg bwt). The HR and HRV of 12 dogs were recorded 20 min before and after the administration of the anesthetic drugs. Doppler was used to obtain systolic, diastolic, and mean blood pressures.
Results: After anesthetic drug administration, the dogs pre-medicated and inducted with alfaxalone had the lowest HR values as compared with those of other protocols. The HRV low frequency and high frequency power ratio decreased in the dogs pre-medicated and intubated with alfaxalone.
Conclusion: This study demonstrates that alfaxalone preserves the cardiovascular function; and hence, is considered as safe to use for the surgical applicability in dogs.

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Introduction

Heart rate variability (HRV) has been suggested to measure as a noninvasive index for autonomic nervous control [1,2]. Several studies have been reported the response of HRV to many effects on medications and stress in humans and animals [3,4]. The HRV measurements have been used as a predictor of mortality in patients with cardiovascular conditions [5]. The HRV contained time domain and frequency domain; time domain parameters are measured from the peak of N-N intervals or R-R peak of the electrocardiogram (ECG) which can be calculated as SDNN (standard deviation of the N-N intervals). Frequency domain or spectral analysis is measured by transforming ECG into a spectral signal. Previous study showed that the progression of cardiac conditions can be altered by cardiac autonomic activity leading to increase in heart rate (HR) and decrease in HRV [6,7].

Morbidity, mortality, and complications due to anesthesia in geriatric and cardiac patients are considerably higher as compared to other medical disciplines [8,9]. Many anesthetic protocols have been developed to improve the outcomes providing the safety for anesthesia in cardiac patients [10,11]. Alfaxalone is a short-acting sedative with a fast onset of effects which is commonly used for inducing short-term anesthesia in patients; advantages of alfaxalone include muscle relaxation and rapid recovery [12]. Previous studies reported that alfaxalone could provide minimal cardiovascular effects in dogs [13]. Alfaxalone is considered safe and especially suitable for the patients suffering from heart disease, hypotension, and old age [14]. Compared with zolazepam and tiletamine or propofol, alfaxalone shows a wider safety margin and greater therapeutic index over other anesthetic agents [15,16]. However, according to various usages of anesthetic agents,

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so far no studies have been performed to analyze the cardiac autonomic activity using HRV to desire anesthetic agents that provided the minimal cardiovascular effects. The objective of this study was to evaluate the effects of various anesthetic agents on cardiac autonomic nervous activity using HRV analysis in dogs and to provide the information for clinical applications. We hypothesized that minimal effects on cardiovascular of anesthetic agents in a dog can be characterized by cardiac autonomic activity using HR and HRV analysis.

Animals

Twelve client-owned dogs aged 3.9 ± 1.0 years and weighing 15.0 ± 2.3 kg were undergone the surgical procedure at the Kasetsart University Veterinary Teaching Hospital, Kamphaeng Saen. The owners of the dogs provided the necessary consents to approve the surgical procedure. The dogs were fasted 12 h prior to the surgery and were randomly assigned to four groups for four anesthetic protocols. The dogs of protocol 1 were pre-medicated and inducted with alfaxalone (at 3 mg/kg bwt). The dogs of protocol 2 anesthetized using zolazepam + tiletamine (at 5 mg/kg bwt). Similarly, diazepam (at 0.3 mg/kg bwt) + ketamine (at 5 mg/kg bwt) were used in protocol 3, and diazepam (0.3 mg/kg bwt) + propofol (at 5 mg/kg) were used in protocol 4. Then, all the dogs were maintained under anesthesia for approximately 1 h with a continuous infusion of 2% isoflurane with an oxygen flow rate of 1 l/min. All the parameters were recorded continuously for further analysis using a blinded assessment.

Clinical evaluations

Routine laboratory evaluations (hematology and serum biochemistry analysis) were performed, as shown in Table 1. The ECG was recorded to evaluate the HR and HRV (Figure 1). Echocardiography was performed in parasternal long axis, short axis and apical four-chamber views in right and left parasternal positions. Echocardiographic images were captured and stored for offline analysis. Left ventricular wall structure and function were calculated by measuring the images from the two-dimensional plane (Figure 2).

HRV measurements

Noninvasive cardiac autonomic nervous control measurements were performed on 12 anesthetized client-owned dogs using a Holter ECG recording device (BTL medical technologies, Thailand). Three electrodes were placed on the shaved skin of the thorax with elastic tape to provide the 20 min ECGs recording for the baseline and 20 min after administering anesthetic drugs. The recorded ECGs from every 10 min sections were averaged and analyzed with analyzing program (BTL medical technologies, Thailand). The HRV was analyzed for the time domain and the frequency domain; time domain parameters were represented as the standard deviation of the R-R interval or SDNN and the frequency domain parameters were expressed as the activity in the high frequency (0.15–0.5 Hz) and low frequency (0.04–0.15 Hz).

Statistical analysis

All data are showed as the mean ± standard error of the mean (mean ± SEM). Statistical analysis was performed using paired *t*-test and one-way ANOVA (GraphPad prism software version 5). A *p*-value of 0.05 or less was indicated for statistical significance.

Results and Discussion

All the 12 dogs received successful surgery without any complications. There were no statistically differences between groups concerning mean age and body weight (p = 0.52 and p = 0.67, respectively). Results of blood profiles and cardiac function before the surgical procedure are summarized in Tables 1 and 2, respectively. Blood profiles and cardiac output in all groups remained within the normal range; there were no significant differences between the groups.

The HR was decreased after the drug administered in almost all groups except for the protocol 2. The dogs in the

Table 1. Blood profiles in four group dogs.

	Protocol 1	Protocol 2	Protocol 3	Protocol 4	Reference range
WBC (×10^3/ul)	21.6 ± 9.2	18.1 ± 5.8	15.3 ± 2.2	37.8 ± 15.7	6–17
RBC (×10^6/ul)	6.1 ± 0.6	4.6 ± 0.03	7.2 ± 0.2	5.3 ± 0.2	5–9
HGB (g/dl)	12.9 ± 1.1	10.4 ± 0.9	16.6 ± 0.3	11.2 ± 0.4	12–18
HCT (%)	38.0 ± 3.0	31.4 ± 2.1	45.5 ± 0.2	33.5 ± 1.3	30–45
PLT (×10^3/ul)	223.7 ± 8.0	435.7 ± 6.5	207.3 ± 3.7	211.3 ± 9.8	200–900
PROT (g%)	8.1 ± 0.7	7.8 ± 0.6	7.4 ± 0.2	7.6 ± 0.6	5.3–7.8
Creatinine (mg%)	0.79 ± 0.01	0.86 ± 0.13	0.72 ± 1.0	1.06 ± 0.6	<1.8
ALT (IU/l)	62.5 ± 2.4	55.0 ± 1.8	66.0 ± 4.2	21.0 ± 0.1	<89

Data represented as mean ± SEM
WBC = white blood cell, RBC = red blood cell, HGB = hemoglobin, HCT = hematocrit, PLT = platelet, PROT = total protein, ALT = Alanine aminotransferase

group of protocol 1 had the highest HR values (149 ± 0.8 beats/min), and the dogs in the group of protocol 4 had the lowest HR (140 ± 11.3 beats/min), as shown in Table 3. The mean blood pressure (MBP) was decreased but remained within the normal range in almost all protocols; however, the MBP due to protocol 4 was significantly decreased ($p < 0.05$). The SDNN significantly decreased after anesthetic drug administration in the group of protocol 2 (Table 4) which indicated a reduction in parasympathetic tone related to the slight increase in the HR in this group. The highest values of low frequency (LF) power were found in the group of protocol 2 which indicated a vagal

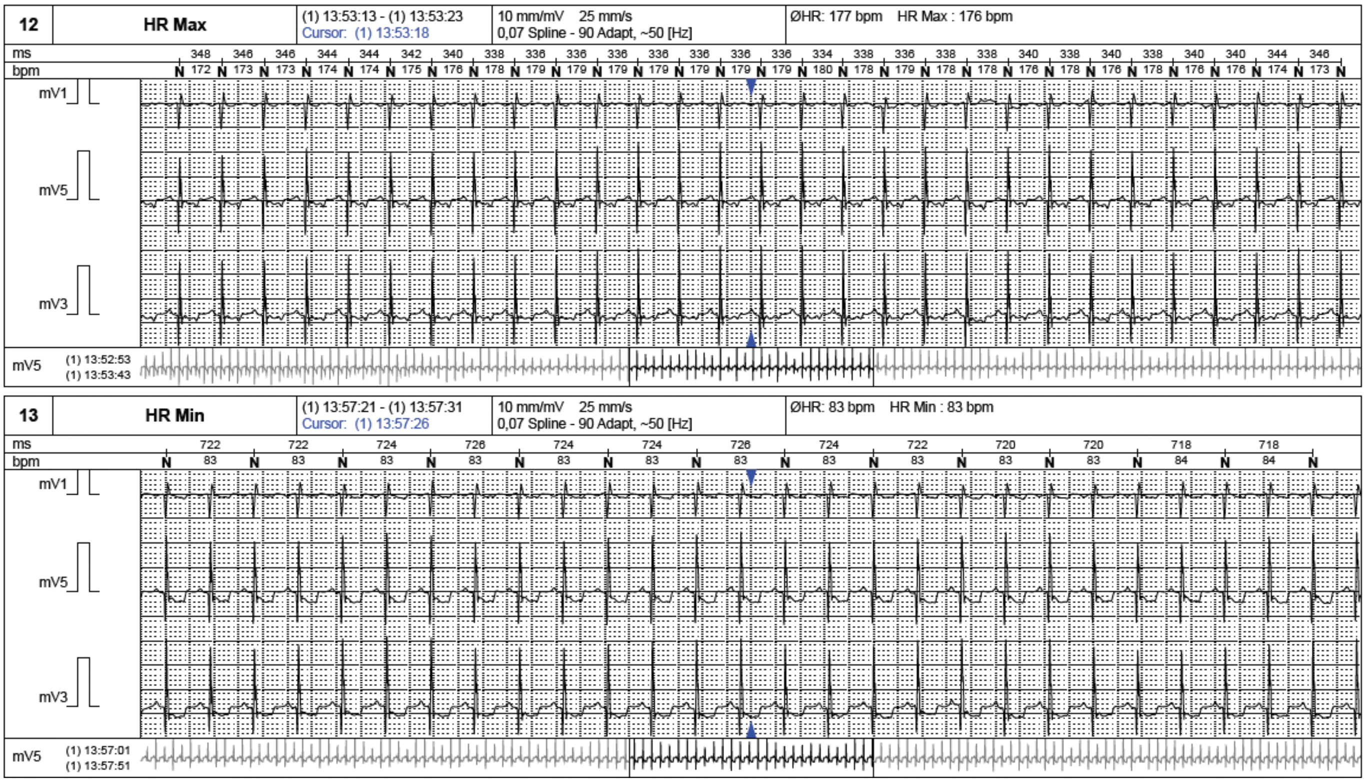

Figure 1. A section of ECG signal obtained from Holter ECG recording.

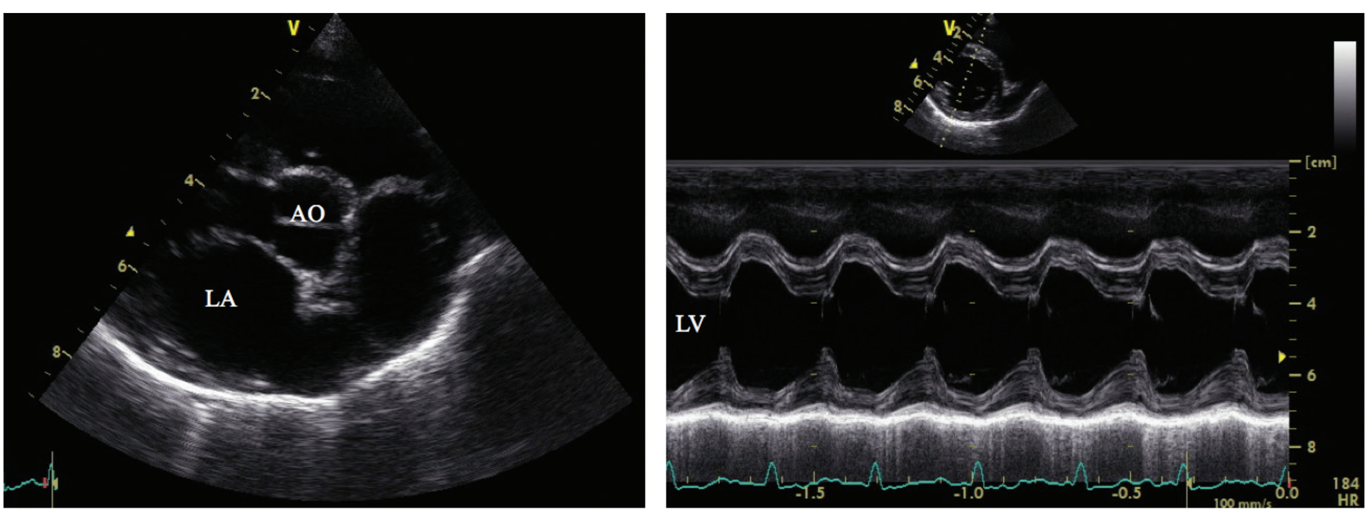

Figure 2. Echocardiographic of transverse image of heart base (left) and M mode image of the left ventricle (right); AO= Aorta, LA = left atrium, and LV = left ventricle.

Table 2. Echocardiagraphic parameters in four groups of protocols.

Parameters	Protocol 1	Protocol 2	Protocol 3	Protocol 4	Reference range
IVSd (cm)	0.75 ± 0.04	1.1 ± 0.2	0.85 ± 0.05	0.87 ± 0.2	0.4–0.9
LVIDd (cm)	1.4 ± 0.08	3.8 ± 1.3	1.5 ± 0.2	2.5 ± 1.5	2.0–2.5
LVPWd (cm)	0.85 ± 0.1	1.0 ± 0.2	0.75 ± 0.04	0.8 ± 0.2	0.4–0.9
IVSs (cm)	0.8 ± 0.04	1.2 ± 0.3	0.8 ± 0.1	0.8 ± 0.3	0.6–1.2
LVIDs (cm)	1.1 ± 0.3	2.9 ± 0.9	1.0 ± 0.2	1.9 ± 1.2	1.2–2.1
LVPWs (cm)	0.8 ± 0.1	1.0 ± 0.1	0.8 ± 0.03	0.9 ± 0.2	0.7–1.3
EF (%)	71.5 ± 0.4	53.0 ± 6.2	78.5 ± 3.6	77.0 ± 5.6	49–81
FS (%)	37.5 ± 0.5	25.0 ± 1.7	43.5 ± 3.7	37.0 ± 3.6	25–45
LA/Ao Ratio	1.5 ± 0.04	1.62 ± 0.07	1.36 ± 0.08	1.5 ± 0.1	1.0–1.5
EPSS (cm)	0.2 ± 0.08	0.6 ± 0.08	0.23 ± 0.08	0.4 ± 0.2	0.4–0.75

Data represented as mean ± SEM
IVSd = diastolic interventricular septum thickness, IVSs = systolic interventricular septum thickness, LVIDd = left ventricular end diastolic diameter, LVIDs = left ventricular end systolic diameter, LVPWd = left ventricular wall diastolic thickness,
LVPWs = left ventricular wall systolic thickness. The left ventricular ejection fraction (EF); EPSS = E point of septum separation

Table 3. The baseline of respiratory and cardiovascular parameters in four groups of protocols.

	Protocol 1	Protocol 2	Protocol 3	Protocol 4	*p* value
RR	28.3 ± 6.0	15.0 ± 2.8	13.0 ± 1.5	19.3 ± 3.5	0.08
HR	149 ± 0.8	145 ± 11.3	145.6 ± 17.5	140 ± 11.3	0.95
SDNN	110 ± 31.6	108 ± 16.3	106.6 ± 48.6	83.0 ± 28.7	0.92
LF/HF	0.72 ± 0.14	1.0 ± 0.2	0.89 ± 0.09	0.88 ± 0.2	0.71
SBP	115.0 ± 20.2	116.0 ± 12.0	140.0 ± 20.0	145.0 ± 5.0	0.19
DBP	66.6 ± 12.0	63.3 ± 5.7	103.3 ± 21.6	93.3 ± 12.6	0.17
MBP	86.6 ± 16.6	86.6 ± 13.3	111.6 ± 23.5	115 ± 10.4	0.30

Data represented as mean ± SEM
RR = respiratory rate, HR = heart rate, SDNN = standard deviation of the N-N intervals, LF/HF = low frequency per high frequency ratio,
SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure
$p < 0.05$ compared among group of protocols

Table 4. HR, HRV, and MBP parameters in four groups of protocols.

		Protocol 1	Protocol 2	Protocol 3	Protocol 4
HR	Baseline	149.0 ± 0.8*	145.0 ± 11.3	145.6 ± 17.5	140.0 ± 11.3
	After surgical	106.0 ± 12.1*	145.7 ± 20.7	117.6 ± 12.3	134.6 ± 22.6
SDNN	Baseline	110.0 ± 31.6	108.0 ± 16.3*	106.6 ± 48.6	83.0 ± 28.7
	After surgical	106.6 ± 69.6	46.5 ± 4.5*	110.3 ± 70.2	128.3 ± 58.6
LF	Baseline	0.17 ± 0.06	0.27 ± 0.2	0.15 ± 0.02	0.13 ± 0.02
	After surgical	0.16 ± 0.06	0.07 ± 0.04	0.45 ± 0.35	0.09 ± 0.03
HF	Baseline	0.61 ± 0.2	0.25 ± 0.1	0.16 ± 0.03	0.16 ± 0.01
	After surgical	0.4 ± 0.1	0.09 ± 0.02	0.42 ± 0.3	0.09 ± 0.04
LF/HF	Baseline	0.72 ± 0.14	1.0 ± 0.2	0.89 ± 0.09	0.88 ± 0.2
	After surgical	0.66 ± 0.1	0.95 ± 0.3	0.99 ± 0.24	1.15 ± 0.2
MBP	Baseline	86.6 ± 16.6	86.6 ± 13.3	111.6 ± 23.5	115 ± 10.4*
	After surgical	61.6 ± 7.2	76.6 ± 6.6	110.0 ± 10.0	78.3 ± 10.1*

Data represented as mean ± SEM
HRV = heart rate variability, HR = heart rate, SDNN = standard deviation of the N-N intervals, LF = low frequency, HF = high frequency,
LF/HF = low frequency per high frequency ratio, MBP = mean blood pressure
*$p < 0.05$ compared with baseline

inhibition. The results from this study showed that zolazepam + tiletamine or Zoletil (protocol 2) produced an increase in HR and had an effect on the parasympathetic activity. The highest values of high frequency (HF) power were found in the group of protocol 1 indicated a high parasympathetic activity, and dogs in this group also had low values of the LF/HF ratio when compared with other protocols. This finding is similar to the previous report that the LF/HF ratio is usually low in a healthy person with sympatho-vagal balance [17]. The results suggested that alfaxalone might preserve the cardiac autonomic activity balance. However, there were no marked HRV results on frequency domain variation were observed in any protocols. The results indicated that the ability of ECG Holter device to measure the frequency domain of the HRV in dogs was not substantially affected by the choice of anesthetic protocols. However, the anesthetized dog was significantly influenced by the HR and blood pressure (Table 4). An insufficient number of dogs in each group could affect the statistical analysis and this is the limitation of this study. Furthermore, only one set of ECG was recorded during 20 min, a recording at different periods of the surgical protocol may affect the results. HRV analysis in anesthetized dogs still requires further investigations to ensure validity for use in the future application.

Conclusions

The findings of this study show that alfaxalone can be used as a pre-medication and intubation in dogs which produce less effect on cardiovascular function than other protocols. The results suggest alfaxalone can be used for cardiovascular stability in dogs during anesthesia.

Acknowledgment

Nothing to disclose.

Conflict of Interest

There is no conflict of interest.

Authors' contributions

All the authors contributed equally.

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