

Effects of alfaxalone on echocardiographic examination in healthy dogs

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Abstract : This study evaluated the effects of alfaxalone (3 mg/kg, intravenously) on echocardiographic examination in healthy dogs using echocardiography. Six adult Beagle dogs were used for this study. Left ventricular dimensions with systolic indexes, trans-blood flow at all cardiac valvular annulus and trans-mitral tissue Doppler values were measured from routine transthoracic echocardiography. Although the changes were not statistically significant, heart rate, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, peak velocities of tricuspid A-wave and transpulmonic flow were increased after alfaxalone induction, while systolic blood pressure, fractional shortening, left ventricular ejection fraction, peak velocities of mitral E-wave, mitral A wave, tricuspid E-wave, transaortic flow and medial e'-, a'- and s'-peaks decreased after alfaxalone induction. No dogs showed hypoxemia during sedation, regardless of intubation and oxygen supply. Although alfaxalone showed mild cardiovascular depression, this protocol could be a good alternative sedative protocol for echocardiographic examination in healthy dogs because the cardiovascular depression was statistically and clinically insignificant. However, further studies in dogs with heart diseases should be conducted to confirm these findings after alfaxalone induction.

Keywords : alfaxalone, canine, cardiac function, cardiovascular depression, left ventricle

Introduction

Alfaxalone (3 α -hydroxy-5 α -pregnane-11,20-dione) is a recently developed neurosteroid injectable anesthetic agent that is gaining popularity for anesthetic induction in dogs and cats [3, 4, 14]. Alfaxalone binds to the gamma amino butyric acid sub-type A receptor in the central nervous system and exerts anesthetic action by modulation of chloride ion transport [4, 14]. Alfaxalone has been safely administered concomitantly with a range of drugs commonly used perioperatively, in order to improve quality of anesthesia and to increase duration of anesthesia in dogs [1, 2, 5-9]. Furthermore, alfaxalone is known to have little or no cardiovascular effects when given at clinical dose rates [15], although premedication with α_2 -adrenoceptor agonists (e.g., medetomidine and dexmedetomidine) can markedly increase the duration of anesthesia in a dose-dependent fashion [2, 10]. Although the pharmacological effect of alfaxalone has been extensively investigated in dogs, studies on its effects on echocardiographic parameters in dogs are still insufficient. Therefore, in this study, we evaluated the effect of alfaxalone on echocardiographic measurement in healthy dogs.

Materials and Methods

Animals

Approval from the animal ethics committee of Kangwon National University was obtained for this experiment prior to the commencement of this study. Six adult Beagle dogs (three males and three females in mean body weight 8.3 ± 3.1 kg and mean age 4.1 ± 1.7 yr) were used for this study. All dogs were healthy based upon physical examination, an electrocardiogram, serum chemistry, hematologic analyses, and diagnostic imaging studies including thoracic radiography and echocardiography (data not shown). Systolic arterial blood pressure was measured at right cranial limb between carpal and elbow joints using a Doppler flow detector (811B; Parks Medical Electronics, USA). Saturation of peripheral oxygen (SpO₂) was monitored using a hand-held pulse oximeter (MP110P; MEK-ICS, Korea) during sedation.

Echocardiographic examination

A complete routine transthoracic echocardiographic examination was performed on each dog with an ultrasound machine (X-300; Siemens, Germany) equipped with a 3.0-9.0 MHz sector transducer, as described in elsewhere [15].

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Table 1. Changes of echocardiographic measurement before (T0), 3 min after (T3) and after recovery (T30) of anesthesia with 3 mg/kg of alfaxalone (A), alfaxalone with intubation (AI), and alfaxalone with intubation supplied with 100% oxygen (AIO) in healthy dogs (n = 6)

		T0	T3	T30
HR (/min)	A	108 ± 19.1	118 ± 14.3	109 ± 22.7
	AI	111 ± 14.5	138 ± 12.4*	122 ± 12.8
	AIO	113 ± 20.3	128 ± 22.5	114 ± 10.6
SAP (mmHg)	A	151.7 ± 1.5	137.7 ± 11.2	131.7 ± 21.0
	AI	153.2 ± 9.6	123.9 ± 20.1	143.7 ± 9.7
	AIO	152.1 ± 11.7	127.3 ± 17.4	132.4 ± 15.5
LVIDd (mm)	A	31.4 ± 0.9	32.3 ± 1.7	31.7 ± 1.3
	AI	30.9 ± 0.6	30.1 ± 1.1	30.5 ± 0.8
	AIO	32.1 ± 1.1	32.3 ± 1.4	31.7 ± 0.5
LVIDs (mm)	A	19.4 ± 1.2	21.7 ± 2.3	19.9 ± 2.1
	AI	19.9 ± 0.4	18.9 ± 1.1	18.3 ± 1.2
	AIO	19.5 ± 1.1	19.7 ± 1.5	19.9 ± 2.3
%FS	A	38.2 ± 5.2	32.8 ± 6.8	37.2 ± 5.1
	AI	35.6 ± 7.5	37.2 ± 4.1	40 ± 3.1
	AIO	39.2 ± 3.5	39 ± 3.7	37.2 ± 2.1
%LVEF	A	61.9 ± 9.4	57.3 ± 18.9	62.7 ± 20.3
	AI	66.4 ± 7.1	64.3 ± 13.2	67.1 ± 9.1
	AIO	62.3 ± 11.6	60.7 ± 8.8	61.1 ± 12.3
MV E-peak (m/s)	A	0.65 ± 0.05	0.44 ± 0.16	0.59 ± 0.13
	AI	0.63 ± 0.06	0.53 ± 0.17	0.62 ± 0.21
	AIO	0.64 ± 0.03	0.54 ± 0.11	0.54 ± 0.19
MV A-peak (m/s)	A	0.49 ± 0.20	0.39 ± 0.27*	0.41 ± 0.29
	AI	0.53 ± 0.17	0.55 ± 0.21	0.51 ± 0.11
	AIO	0.51 ± 0.12	0.54 ± 0.18	0.40 ± 0.24
TV E-peak (m/s)	A	0.24 ± 0.11	0.21 ± 0.11	0.18 ± 0.09
	AI	0.22 ± 0.14	0.27 ± 0.17	0.28 ± 0.10
	AIO	0.20 ± 0.04	0.25 ± 0.14	0.28 ± 0.16
TV A-peak (m/s)	A	0.26 ± 0.02	0.37 ± 0.05*	0.20 ± 0.08
	AI	0.27 ± 0.10	0.35 ± 0.08*	0.34 ± 0.11*
	AIO	0.24 ± 0.14	0.28 ± 0.06	0.31 ± 0.08
AO-peak (m/s)	A	0.94 ± 0.19	0.78 ± 0.11	0.91 ± 0.17
	AI	1.04 ± 0.17	0.84 ± 0.26	0.97 ± 0.11
	AIO	0.98 ± 0.21	0.84 ± 0.27	0.94 ± 0.23
PA-peak (m/s)	A	0.77 ± 0.17	0.83 ± 0.11	0.91 ± 0.19
	AI	0.74 ± 0.21	0.79 ± 0.09	0.88 ± 0.13
	AIO	0.75 ± 0.19	0.81 ± 0.29	0.78 ± 0.31
Medial e' (cm/s)	A	6.7 ± 1.0	5.7 ± 1.4	6.6 ± 0.8
	AI	6.8 ± 1.7	4.8 ± 2.7	6.8 ± 1.1
	AIO	7.1 ± 0.8	6.1 ± 1.4	7.3 ± 2.1
Medial a' (cm/s)	A	6.4 ± 2.3	7.3 ± 2.4	5.4 ± 3.1
	AI	6.0 ± 1.4	7.0 ± 1.1	6.3 ± 2.3
	AIO	7.1 ± 2.7	6.1 ± 3.3	5.9 ± 2.7
Medial s' (cm/s)	A	7.7 ± 2.3	7.3 ± 3.0	8.2 ± 1.1
	AI	7.3 ± 3.1	5.8 ± 2.2	7.3 ± 3.9
	AIO	7.5 ± 1.5	7.1 ± 2.6	6.5 ± 3.7

*Statistically different from baseline T0, ($p < 0.05$). HR, heart rate; LVIDs, left ventricular end-systolic diameter; LVIDd, left ventricular end-diastolic diameter; %LVEF, left ventricular ejection fraction; %FS, fractional shortening; MV E-peak, peak velocity of mitral E-wave; MV A-peak, peak velocity of mitral A wave; TV E-peak, peak velocity of tricuspid E-wave; TV A-peak, peak velocity of tricuspid A wave; AO-peak, peak velocity of transaortic flow; PA-peak, peak velocity of transpulmonic flow.

Measurements were taken by using two-dimensional guided M-mode on the standard right parasternal short-axis view at the level of the chordae tendineae for measurement of the left ventricular (LV) dimension. Heart rate (HR) was also calculated based on R-R interval determined from a simultaneous lead II electrocardiogram. All M-mode measurements were performed in accordance with the recommendations of the American Society of Echocardiography [13] and the Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine [16]. Doppler studies including tissue Doppler imaging were performed from either the left apical five-chamber view (mitral and aortic) or the left cranial parasternal location (pulmonic). Transmitral peak velocities of early (E wave) and late (A wave) diastole were acquired at the tips of the mitral valve leaflets, while transtricuspid peak velocities of early (E wave) and late (A wave) diastole were acquired at the tips of the tricuspid valve leaflets, using left apical long axis planes. Aortic peak velocity was also measured at left apical 5 chamber plane, while pulmonic peak velocity was measured at right parasternal short axis of pulmonic valve location. To assess LV diastolic function, tissue Doppler imaging velocities were obtained on the septal (medial) corner of the mitral annulus, including the peak systolic (s'), and early (e') and late annular velocities (a'). Before administration of drugs, a catheter (22 or 24 gauge, BD Angiocath; Becton, Dickinson and Company, USA) was placed in a cephalic vein in each dog. All echocardiographic measurements were recorded in the conscious animal (baseline; T0), at 3 min after administration of alfaxalone (3 mg/kg, intravenously, Alfaxan; Jurox, Australia; T3; slowly bolus injection), and after recovery from anesthesia (T30). After induction, all dogs breathed room air without an endotracheal intubation (experiment A). After one-day washout period, the experiment was repeated with the previous method, except that all dogs were intubated without oxygen supply (experiment AI), and intubated with 100% oxygen supply (experiment AIO). All dogs were extubated, if dogs showed either gagging or swallowing. Tracheas were desensitized with 2% lidocaine spray when intubated. Duration of sedation was recorded as the time from lateral recumbency to extubation, as described in elsewhere [14]. Time to recovery was calculated as the time from lateral recumbency to standing, as described in elsewhere [14].

Statistical analysis

Statistical analyses were performed using commercially available a statistical software. Normal distribution was confirmed by Kolmogorov–Smirnov test. Continuous variables were presented as mean \pm SD. A repeated measurement via one-way ANOVA was used to investigate differences from baseline values with a post hoc Tukey–Kramer multiple comparisons test. For all tests, $p < 0.05$ was considered significant.

Results

Sedation duration was 13.8 ± 4.6 min, while recovery time was 17.7 ± 5.6 min calculated as the time from lateral recumbency to standing. SpO₂ was maintained 97–99% in all dogs in this experiment. HR, left ventricular end-systolic diameter (LVIDs), left ventricular end-diastolic diameter (LVIDd), peak velocities of tricuspid A-wave (TV A-peak) and transpulmonic flow (PA-peak) were increased after alfaxalone induction (T3) and returned to baseline value after recovery (T30) in all experiments, although there were no significant differences among 3 experiments except HR in AI group at T3 ($p = 0.021$), TV A peaks in A and AI groups at T3 ($p = 0.011$) and AI group at T30 ($p = 0.025$), and before and after alfaxalone administration. The systolic blood pressure (SAP), fractional shortening (%FS), left ventricular ejection fraction (%LVEF), peak velocities of mitral E-wave (MV E-peak), mitral A wave (MV A-peak), tricuspid E-wave (TV E-peak), transaortic flow (AO-peak), medial e' -, a' - and s' -peaks were decreased after alfaxalone induction (T3) and returned to baseline value after recovery (T30) in all experiments, although there were no significant differences among 3 experiments except MV A peak in A group at T3 ($p < 0.05$), and before and after alfaxalone administration (T3; Table 1).

Discussion

Although sedation is not necessary for echocardiographic examination in most cases, light sedation is often required for furious or un-cooperated dogs. According to Veterinary Information Networks (VIN), several sedation protocols in dogs included 0.3 mg/kg of butorphanol and 0.3 mg/kg of diazepam intravenous (IV) combination, 0.005 mg/kg of acepromazine and 0.01 mg/kg of buprenorphine IV combination, 0.3 mg/kg of butorphanol and 0.15 mg/kg of midazolam IV combination, and 0.05 mg/kg of acepromazine and 0.05 mg/kg of butorphanol combination have been suggested for echocardiographic examination [11]. Durations of sedative effect in most protocols described in VIN was 15–20 min. The sedative effect of alfaxalone in dogs of our study was 12–17 min as similar to other sedative protocols, suggesting a possible alternative sedative protocols for echocardiographic examination.

Several studies found that alfaxalone produced good to excellent short-term anesthesia even in unpremedicated dogs with minimal adverse effects [1, 2, 7, 8]. One study also found cardiorespiratory effects of alfaxalone were dose dependent, with high doses producing increased cardiopulmonary depression in dogs [6]. Furthermore, the recommended dose of alfaxalone rarely induced cardiopulmonary suppression in dogs [5, 6, 12, 14]. Prior to this study, we performed a pilot study with 3 toy breed dogs. One dog showed a significant reduction in SAP and HR after alfaxalone administration. The LV diastolic and systolic performances were significantly decreased (data not shown). Since these dogs were not intubated during echocardiographic examination, we suspected

the hypoventilation and hypoxemia might be the cause of cardiorespiratory depression. Several studies also found dose-dependent respiratory depression after alfaxalone administration [6, 9]. Hypoxemia could induce a significant reduction of myocardial contractibility. We presumed myocardial depression in only one dog in our pilot study due to hypoxemia (because all dogs breathed room air without intubation during anesthesia) with dose-dependent respiratory depression from alfaxalone administration. Since intubation supplied with 100% oxygen could be a good option to reduce hypoxemia, we evaluated the effect of alfaxalone in dogs with/without intubation and oxygen supply.

Our study also found that 3 mg/kg of alfaxalone (recommended dose for unpremedicated dogs) did not induce a significant cardiovascular depression, although the SAP and LV systolic and diastolic performance was slightly reduced. Muir *et al.* [6] found that cardiac output did not change or increased minimally after the IV administration of 6 mg/kg of alfaxalone (higher than our study dose). Authors presumed that this effect might be due to a transient increase in HR and small decreases in peripheral vascular resistance (decreased afterload) secondary to peripheral vasodilation as suggested by other [5]. Our study showed mild increased TV A-peak and PA-peak along with mild decreased LVIDd and AO-peak, suggesting increased venous return in the right cardiac chamber. Alfaxalone might induce sympathetic activation of veins, causing to decrease venous compliance along with increasing vasomotor tone. This effect might promote venous return indirectly by augmenting cardiac output through the Frank-Starling mechanism. To summarize the effect of alfaxalone on echocardiographic examination, TV-A peak and PA-peak were mildly increased, possibly due to increased right ventricular preload from increased venous return. Mildly increased LVIDs and LVIDd might be due to increased LV preload from increased pulmonic flow, while mildly decreased AO-peak, and medial e', a'- and s'-peaks on tissue Doppler might be due to increased LV afterload and wall stress by vasoconstriction.

No study evaluated LV diastolic function in dogs after alfaxalone administration, to date. Reduced medial e', a' and s'-peaks on tissue Doppler in this study suggested decreased LV diastolic function by alfaxalone, although it was transient and was clinically insignificant. Increased LV afterload and wall stress by vasoconstriction might be the cause for impairment of LV diastolic function.

In the present study, unlike our expectation, no dogs showed hypoxemia during sedation, regardless of intubation and oxygen supply. Therefore minimally suppressed cardiovascular function might be due to direct effect from alfaxalone. Increased sympathetic tone evidenced by HR acceleration after alfaxalone administration might induce vasoconstriction via an adrenergic effect, and might be responsible minimal cardiovascular depression in this study.

There are several limitations to the present study. Firstly, the study population was limited to a small number of

healthy colony dogs and could not achieve sufficient statistical power to prove minimal cardiovascular detrimental effects. Secondly, the study dogs were healthy, and thus the study result may be differed in dogs with heart diseases. Thirdly, because the full echocardiography generally took to finish within 10-15 min, we were unable to check the time point between the induction and recovery (*e.g.*, 5-7 min after alfaxalone injection). Lastly, the LV systolic and diastolic function has only been assessed by echocardiography, although this methodology has been associated with potential error in measurement of LV function.

Although our sedative protocol showed mild cardiovascular depression, this protocol might be a good alternative sedative protocol in echocardiographic examination in dog, because the cardiovascular depression was statistically and clinically insignificant.

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