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Autonomic Nervous Properties of Atropine and Glycopyrrolate on Heart Rate Variability during Anesthesia with Ketamine-Xylazine in Dogs

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Abstract : Anticholinergics, which are commonly given as a pre-anesthetic medication to prevent adverse effects in canine anesthesia, can cause cardiac adverse effects. To determine the effects of atropine and glycopyrrolate on the balance of sympathetic nervous tone and parasympathetic nervous tone of the heart during ketamine anesthesia in beagle dogs, heart rate variability (HRV), duration of anesthesia and behavioral changes were evaluated. There were no significant temporal domain differences between atropine and glycopyrrolate. Concerning the frequency domain component, atropine and glycopyrrolate effects were significantly lower ($P < 0.05$) than the control saline-treated group. However, the root mean square of the interval differences between consecutive R peaks (RMSSD) and the standard deviation of Poincare plot perpendicular to the line-of-identity (SD1) in atropine were significantly decreased ($P < 0.05$) from the baseline value, and the low frequency/high frequency ratio (LF:HF ratio) in glycopyrrolate was significantly increased from baseline value ($P < 0.05$). The change of SD1 agreed with that of the high frequency (HF) in the frequency domain component and also with those of respiratory rate and SpO_2-R. Our results prove that glycopyrrolate is more suitable as a pre-anesthetic anticholinergic in ketamine anesthesia of dogs with respect to safety and duration of action.

***Key words* :** anticholinergic, heart rate variability, ketamine, sympathetic nerve, xylazine.

INTRODUCTION

Anticholinergics are commonly given as pre-anesthetic medication for the prevention of reflectory bradycardia and a sudden decrease in blood pressure during anesthesia. However, anticholinergics can cause adverse effects such as excessive tachycardia, ventricular tachycardia, ventricular fibrillation, and acute hemorrhage with myocardial ischemia by direct vagolytic action (3,9).

Atropine is a parasympatholytic drug, which induces direct vagolytic action on the sinoatrial (SA) and atrioventricular (AV) nodes, and inhibition of acetylcholine activity occurs at postganglionic parasympathetic neuroeffector sites, mainly at muscarinic receptors. As atropine readily passes through the blood-brain barrier, a central anticholinergic syndrome such as tachycardia may be produced (15). Typically, the propensity of an anesthetic such as ketamine to produce tachycardia is not routinely indicated (3). Glycopyrrolate, which blocks peripheral muscarinic receptors and inhibits cholinergic transmission, does not cross the blood-brain barrier, and produces only mild tachycardia (1).

Heart rate variability (HRV) has been used as a research tool to evaluate the function of the autonomic nervous system that plays a major role in the control of the cardiovascular system, particularly in the modulation of heart rate (5,13). Although previous studies (2,17) have compared atropine and glycopyrrolate differences in heart rate and HRV, the effects of these anticholinergics on the autonomic nervous system of the heart have been rarely investigated using HRV under anesthesia, by a combination ketamine and xylazine that is generally used in dogs.

The aim of the present study was to identify safer anticholinergics; to do this, we compared the effects of atropine and glycopyrrolate on HRV during ketamine-xylazine anesthesia in dogs.

Materials and Methods

Experimental animals and conditions

All experimental procedures and animal protocols were carried out in accordance with the requirements of the Guide for Care and Use of Laboratory Animals of The Seojeong College. After approval of the institutional and ethics committee, seven beagle dogs (four male and three female,

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weight 10.2 ± 2.1 kg) aged from 2–4 years were included in the study. The dogs were housed with controlled light/dark cycle (light on from 6:00 a.m. to 6:00 p.m.), an ambient temperature of 21°C–25°C and unlimited access to standard laboratory dog diet and water. The animals were fasted except for ad libitum water for 12 h before anesthetic application. All experiments were carried out with healthy dogs under standardized experimental conditions, slightly dimmed laboratory lighting and thermo-neutral temperature (22°C–25°C). The experiments always began at 4:00 p.m. and dogs remained unrestrained in a small room. The animals were assigned to three different experimental groups corresponding to anticholinergics: atropine (A, n = 7), glycopyrrolate (G, n = 7), and saline (S, n = 7). Each dog randomly received atropine and glycopyrrolate with an intervening time of 1 week, using a crossover experimental design, so that each dog served as its own control.

Heart rate variability measurement

To obtain a HRV raw data, the recorder was fitted to the dog's thorax and allowed to stabilize for 15 min. After observing a stable heart rate, pretreatment raw data was recorded for 5 min. Atropine (Atropine sulfate®; 0.022 mg/kg, Daihan Pharm, Seoul, Korea), glycopyrrolate (Tabinul®; 0.011 mg/kg, Hana Pharm, Seoul, Korea), or saline (0.9% NaCl®; 0.1 m*l*/kg, Daihan Pharm, Seoul, Korea) was then administered intramuscularly. Five min later, the HRV was recorded for 5 min. After 15 min, xylazine (Rompun 2%®; 2.2 mg/kg, Bayer, Seoul, Korea) was administered intramuscularly and a second HRV was recorded for 5 min. Ketamine (Ketamine 50 inj. ®; 11 mg/kg, Yuhan Corp., Seoul, Korea) was administered intravenously at 10 min after xylazine administration. After ketamine was administered (0 min), HRV raw data were recorded for 5 min at 0, 5, 10, 20, 30, 40, 50, 60, 75 and 90 min. Telemetric measurement of heart beat activity (R-R interval) was done using a Polar S-810i device (Polar Electro Co., Kempele, Finland). At the end of each measurement, the stored data was transmitted to a computer via serial interface. The R-R intervals and information about the corresponding autonomic activities of the animal were then analyzed using Polar Pro Trainer software (Polar Electro Co.), which allowed for automatic correction of the recorded tachogram. All files were examined manually for artifacts.

Heart rate variability analyses

Artifact-free HRVsignals analyzed over a period of 5 min during steady state conditions were analyzed by HRV analysis software v 1.1 (Biomedical Signal Analysis Group, Kuopio, Finland). HRV raw data was analyzed in the time domain and the frequency domain. In the time domain components, the square root of variance of all R-R intervals (SDNN), root mean square of successive differences of R-R intervals (RMSSD), heart rate (HR), 50 percent normal beat to normal beat (NN) from the common number of successive pairs of intervals that differed for more than 50 ms received for all the record period (pNN 50) and R-R triangular index and triangular interpolation of NN intervals (TINN) were calculated. In the frequency domain components by Fast Fourier transform, the power of the very low frequency band (VLF, 0–0.04 Hz), the low frequency (LF, 0.04–0.15 Hz), the high frequency (HF, 0.15–0.4 Hz), LF/HF ratio, SD 1 and the standard deviation of Poincare plot to the line of identity (SD 2) were calculated.

Recovery time from anesthesia and behavioral changes

To evaluate recovery from anesthesia, the time from administration of ketamine to lifting of the head (HT), to sternal position (ST) and walking (WT) were recorded.

Respiratory rate and oxygen saturation-pulse rate (SpO_2-R)

Respiratory rate and SpO_2-R were determined with a BM3 vet patient monitor (Bionet, Seoul, Korea) at 5, 10, 15 and 20 min following ketamine administration.

Maximum heart rate and peak time

The maximum heart rate (max HR), representing the maximum heart rate during the entire assessed period following the basal period, was determined as the peak time (PT). The time to attain max HR was also measured.

Statistical analysis

An artifact-free 5 min period for each epoch of R-R interval data was used in statistical analysis. The results are expressed as absolute values ($msec^2$ per Hz). Data is expressed as the mean ± SD unless indicated otherwise. The data were analyzed by two-way repeated analysis variance (two-way reapeated ANOVA) followed by the Duncan comparison test as post hoc analysis for heart rate and HRV variables between groups at each time and each group comparisons between values before and after anesthesia. The correlation (r) of coefficients between individuals (SDNN, RMSSD, heart rate, pNN 50, R-R triangular index, TINN, VLF, LF, HF, LF/HF ratio, SD 1 and SD 2) were calculated and compared using a Pearson's correlation test. HT, ST, WT, PT, respiratory rate and SpO_2-R between groups were analyzed using ANOVA followed by the Duncan comparison test as post hoc analysis. A significant difference was defined as $P < 0.05$.

RESULTS

Table 1 summarizes the time domain results for responses to the administration of atropine and glycopyrrolate. There were no differences in basal (B) and anticholinergic administration time (Anti-c) values. However, concerning the xylazine administration time (XYL), SDNN and pNN50 of A group and RMSSD, RR triangular index and TINN of A and G group were statistically lower than the S group values ($P < 0.05$). HR of groups A and G were not statistically dif-

Table 1. The comparison of time domain components among control and anticholinergic administration groups during induction of anesthesia with ketamine-xylazine

Time (min)	SDNN (s)			HR (beat/min)			RMSSD (ms)			pNN50 (%)			RR triangular index		
	A	G	S	A	G	S	A	G	S	A	G	S	A	G	S
B	0.61 ± 0.10^{a}	0.54 ± 0.10^{a}	0.52 ± 0.07^{a}	$112 \pm 38^{a\#}$	$115 \pm 21^{a\#}$	117 ± 19^{a}	$44.6 \pm 50.4^{a\#}$	29.4 ± 13.0^{a}	27.5 ± 8.8^{a}	16.7 ± 22.9^{a}	10.3 ± 9.9^{a}	8.7 ± 5.7^{a}	$0.11 \pm 0.06^{a\#}$	$0.10 \pm 0.03^{a\#}$	0.09 ± 0.02^{a}
Anti-c	0.50 ± 0.04^{a}	$0.60 \pm 0.09^{a\#}$	0.54 ± 0.10^{a}	$127 \pm 29^{a\#}$	$103 \pm 15^{a\#}$	114 ± 20^{a}	20.0 ± 17.9^{a}	27.6 ± 10.8^{a}	27.3 ± 11.8^{a}	5.6 ± 9.3^{a}	9.3 ± 9.7^{a}	9.7 ± 9.8^{a}	0.06 ± 0.01^{a}	$0.09 \pm 0.04^{a\#}$	0.08 ± 0.02^{a}
XYL	0.55 ± 0.11^{a}	$0.72 \pm 0.22^{a,b*\#}$	$0.83 \pm 0.23^{b*\#}$	$128 \pm 45^{b\#}$	$96 \pm 41^{a,b}$	$80 \pm 20^{a*\#}$	12.3 ± 7.2^{a}	25.5 ± 27.1^{a}	$61.8 \pm 29.8^{b\#}$	1.5 ± 1.5^{a}	$10.6 \pm 17.0^{a,b}$	$26.3 \pm 15.7^{b\#}$	$0.03 \pm 0.01^{a*}$	0.06 ± 0.04^{a}	$0.13 \pm 0.04^{b\#}$
0	$0.35 \pm 0.02^{a*}$	$0.43 \pm 0.11^{a,b}$	0.53 ± 0.05^{b}	$178 \pm 25^{b*}$	$150 \pm 36^{b*}$	115 ± 11^{a}	$6.8 \pm 4.6^{a*}$	9.3 ± 8.5^{a}	17.9 ± 7.3^{b}	0.2 ± 0.4^{a}	1.2 ± 2.3^{a}	3.5 ± 4.1^{a}	$0.03 \pm 0.03^{a*}$	$0.03 \pm 0.02^{a*}$	0.05 ± 0.02^{a}
5	0.45 ± 0.02^{a}	$0.54 \pm 0.12^{a,b}$	0.58 ± 0.05^{b}	$135 \pm 18^{b\#}$	$115 \pm 22^{a,b\#}$	104 ± 10^{a}	19.3 ± 12.1^{a}	19.5 ± 14.0^{a}	36.1 ± 5.9^{b}	5.6 ± 7.0^{a}	5.8 ± 8.6^{a}	13.9 ± 5.1^{a}	0.08 ± 0.03^{a}	0.07 ± 0.04^{a}	$0.11 \pm 0.01^{a\#}$
10	$0.55 \pm 0.05^{a\#}$	0.56 ± 0.10^{a}	0.64 ± 0.06^{a}	$112 \pm 24^{a\#}$	$110 \pm 18^{a\#}$	$95 \pm 9^{a*}$	23.8 ± 14.9^{a}	21.4 ± 12.0^{a}	41.8 ± 4.6^{b}	9.2 ± 11.6^{a}	4.8 ± 7.6^{a}	18.9 ± 4.0^{b}	0.06 ± 0.04^{a}	0.06 ± 0.03^{a}	$0.11 \pm 0.02^{b\#}$
20	$0.61 \pm 0.03^{a\#}$	$0.63 \pm 0.09^{a\#}$	$0.72 \pm 0.11^{a*\#}$	$100 \pm 13^{a\#}$	$97 \pm 13^{a\#}$	$86 \pm 12^{a*\#}$	25.3 ± 8.8^{a}	28.0 ± 11.1^{a}	51.0 ± 11.2^{b}	7.0 ± 5.4^{a}	7.9 ± 8.1^{a}	$25.9 \pm 6.4^{b\#}$	0.07 ± 0.01^{a}	0.06 ± 0.03^{a}	$0.11 \pm 0.03^{b\#}$
30	$0.69 \pm 0.05^{a\#}$	$0.63 \pm 0.08^{a\#}$	$0.74 \pm 0.11^{a*\#}$	$90 \pm 15^{a\#}$	$97 \pm 13^{a\#}$	$84 \pm 11^{a*\#}$	$48.5 \pm 27.8^{a,b\#}$	30.5 ± 14.7^{a}	$58.7 \pm 25.9^{a\#}$	$23.6 \pm 18.7^{a\#}$	11.0 ± 11.4^{a}	$28.3 \pm 14.3^{a\#}$	$0.09 \pm 0.03^{a\#}$	0.08 ± 0.03^{a}	$0.10 \pm 0.03^{a\#}$
40	$0.61 \pm 0.05^{a\#}$	$0.65 \pm 0.09^{a\#}$	$0.79 \pm 0.24^{a*\#}$	$103 \pm 20^{b\#}$	$94 \pm 11^{a,b\#}$	$81 \pm 18^{a*\#}$	29.2 ± 28.7^{a}	30.4 ± 20.6^{a}	$67.1 \pm 44.9^{b\#}$	12.7 ± 15.4^{a}	12.1 ± 13.5^{a}	$32.6 \pm 22.9^{a*\#}$	0.06 ± 0.04^{a}	$0.08 \pm 0.03^{a,b}$	$0.12 \pm 0.04^{b\#}$
50	$0.58 \pm 0.04^{a\#}$	$0.70 \pm 0.19^{a\#}$	$0.76 \pm 0.20^{a*\#}$	$105 \pm 15^{a\#}$	$93 \pm 25^{a\#}$	$84 \pm 19^{a*\#}$	20.4 ± 27.3^{a}	$37.9 \pm 23.3^{a,b\#}$	$67.3 \pm 52.4^{b\#}$	8.5 ± 19.5^{a}	17.3 ± 19.6^{a}	$28.2 \pm 22.6^{a\#}$	0.06 ± 0.05^{a}	$0.09 \pm 0.04^{a\#}$	$0.13 \pm 0.07^{a\#}$
60	$0.67 \pm 0.14^{a\#}$	$0.70 \pm 0.15^{a\#}$	$0.79 \pm 0.20^{a*\#}$	$93 \pm 18^{a\#}$	$91 \pm 24^{a\#}$	$82 \pm 21^{a*\#}$	40.5 ± 35.0^{a}	$40.4 \pm 19.2^{a\#}$	$70.3 \pm 46.2^{a*\#}$	19.5 ± 24.2^{a}	$21.1 \pm 12.9^{a\#}$	$35.7 \pm 25.3^{a*\#}$	$0.10 \pm 0.06^{a\#}$	$0.09 \pm 0.04^{a\#}$	$0.14 \pm 0.06^{a\#}$
75	$0.66 \pm 0.16^{a\#}$	$0.68 \pm 0.12^{a\#}$	$0.83 \pm 0.24^{a*\#}$	$96 \pm 23^{a\#}$	$91 \pm 15^{a\#}$	$79 \pm 22^{a*\#}$	$44.8 \pm 32.6^{a\#}$	$41.8 \pm 23.4^{a\#}$	$80.6 \pm 63.0^{a*\#}$	22.4 ± 24.3^{a}	$20.2 \pm 18.7^{a\#}$	$30.5 \pm 24.3^{a*\#}$	$0.10 \pm 0.06^{a\#}$	$0.11 \pm 0.03^{a\#}$	$0.12 \pm 0.03^{a\#}$
90	$0.59 \pm 0.16^{a\#}$	$0.71 \pm 0.17^{a\#}$	$0.73 \pm 0.12^{a*\#}$	$109 \pm 29^{a\#}$	$89 \pm 20^{a\#}$	$85 \pm 17^{a*\#}$	35.9 ± 31.8^{a}	$46.2 \pm 28.0^{a\#}$	54.1 ± 24.1^{a}	16.6 ± 20.8^{a}	$25.0 \pm 18.4^{a\#}$	$29.5 \pm 18.4^{a*\#}$	$0.10 \pm 0.05^{a\#}$	$0.11 \pm 0.04^{a\#}$	$0.13 \pm 0.04^{a\#}$

B: base line. Anti-c: atropine, glycopyrrolate and saline. XYL: xylazine. SDNN: square root of variance of all R-R intervals. RMSSD: root mean square of successive differences of R-R intervals. HR: heart rate. pNN 50: Percent of difference between adjacent normal RR intervals that are greater than 50 msec. TINN: triangular interpolation of NN intervals. A: Group atropine. G: Group glycopyrrolate. S: Group control. [ab]Means with different letters are statistically different among groups ($P < 0.05$) .[*]Significantly different from base line values ($P < 0.05$). [#]Significantly different from 0 (after ketamine administration) ($P < 0.05$).

ferent ($P < 0.05$). However, HR of group A was statistically higher ($P < 0.05$) than that of the S group. After ketamine administration, SDNN, RMSSD, pNN50 and RR triangular index of groups A and G were statistically lower than S ($P < 0.05$). However, HR was statistically higher ($P < 0.05$) in groups A and G than in the S group. There was no statistically significant difference between the A and G groups in the time domain frequency.

Concerning the frequency domain components, no differences among groups for VLF, LF, HF and LF/HF were found, with the exception of LF at 10 min, and the differences which were statistically lower than G and S, and A and G in HF at 0 min were statistically lower than S ($P < 0.05$). SD1 of groups A and G were statistically lower than S between XYL and 30 min, and A in SD2 was statistically lower than S at each XYL and 10 min ($P < 0.05$). There were no statistically significant differences in RR and SpO_2-R except for A, G in RR at 10 min was statistically lower than S, and A and G in SpO_2-R at 30 min were statistically higher than S ($P < 0.05$). Generally, A values were lower than G and S values, and G values were lower than S values in all parameters. Statistical analysis and descriptive statistics of the variables of the frequency domain, RR and SpO_2-R are summarized in Table 2.

Comparisons of the SDNN, RMSSD, HR, pNN50, RR triangular index, TINN, SD 1, SD 2, VLF, LF, HF and LF/HF for all experiments in each group revealed significant correlations. However, the statistical difference among groups was not founded (Fig 1). In A, $r > 0.4$ was found among SDNN, RMSSD, pNN50, RR triangular index, TINN, SD 1, SD 2, VLF, LF and HF, as well as between HR and LF/HF ($P < 0.01$). In G, $r > 0.4$ was found among all parameters except for HR and LF/HF ($P < 0.01$). The r between VLF or HF and LF/HF for all groups were negative ($r < -0.05$) ($P < 0.01$).

In comparisons of HT, ST, WT and PT among groups, excluding A and G, which were statistically higher than S in max HR, no statistical differences were found (Table 3, 4).

DISCUSSION

The purpose of the study was to evaluate the properties of

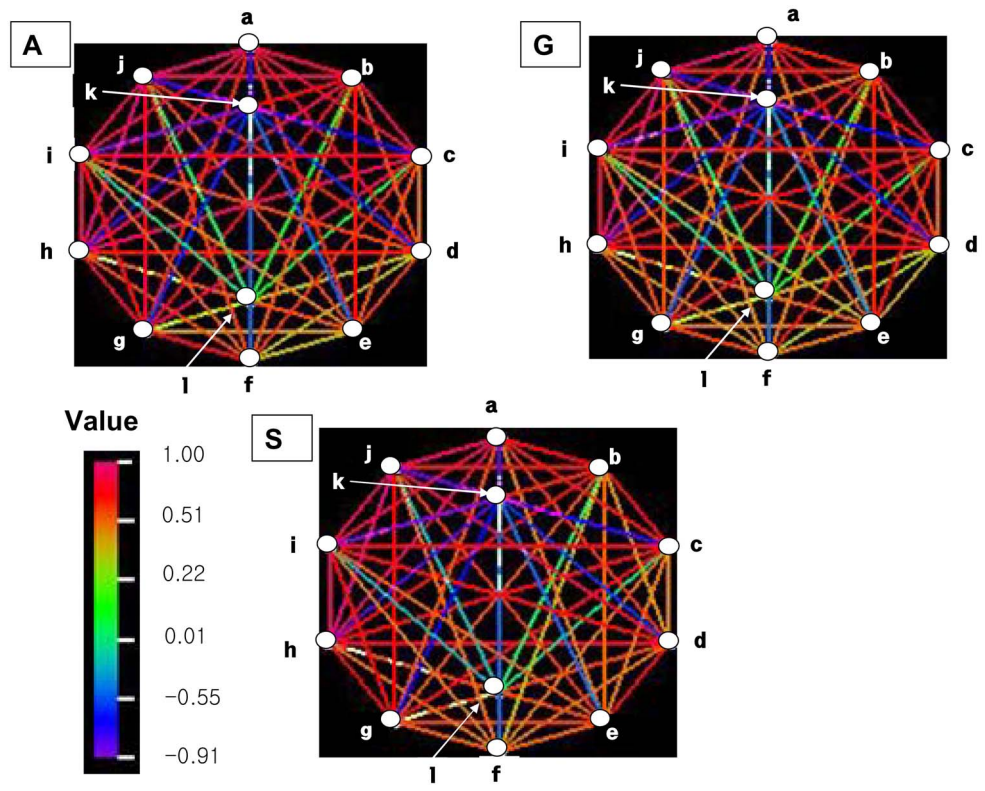

Fig 1. The Correlations among HRV components in each group after ketamine administration. The statistical differences among groups are not showed. The color scale indicates the degree of correlation (Color change toward dark red indicates strong correlation, and that toward dark violet indicate weak correlation). a: percent of difference between adjacent normal RR intervals that are greater than 50 msec (pNN 50). b: normal beat to normal beat triangular index (RR triangular index). c: triangular interpolation of NN intervals (TINN). d: high frequency (HF). e: low frequency (LF). f: very low frequency (VLF). g: the standard deviation of poincare plot to the line-of- identity (SD2). h: the standard deviation of poincare plot perpendicular to the line-of- identity (SD1). i: square root of variance of all R-R intervals (SDNN). j: root mean square of successive differences of R-R intervals (RMSSD). k: heart rate (HR) . l: low frequency/high frequency ratio (LF/HF). A: Group atropine. G: Group glycopyrrolate. S: Group control.

Table 2. The comparison of frequency domain components among control and anticholinergic administration groups during induction of anesthesia with ketamine-xylazine

Time (min)	VLF (ms^2)			LF (ms^2)			HF (ms^2)			LF/HF (ratio)			SD1 (ms)			SD2 (ms)		
	A	G	S	A	G	S	A	G	S	A	G	S	A	G	S	A	G	S
B	533 ± 596[a]	559 ± 462[a]	354 ± 202[a]	310 ± 170[a]	485 ± 437[a]	402 ± 246[a]	123 ± 79[a]	148 ± 123[a]	118 ± 42[a]	2.9 ± 0.9[a]	3.6 ± 1.4[a]	3.1 ± 1.0[a]	34 ± 38.1[a#]	22.6 ± 9.1[a]	21.4 ± 6.3[a]	139.9 ± 122.0[a]	103.3 ± 40.2[a]	86.1 ± 37.2[a]
Anti-c	388 ± 442[a]	482 ± 280[a]	290 ± 179[a]	139 ± 112[a]	307 ± 230[a]	303 ± 154[a]	66 ± 71[a]	79 ± 71[a]	142 ± 101[a]	4.1 ± 3.6[a]	4.7 ± 2.1[a]	2.4 ± 0.8[a]	15.0 ± 12.8[a]	20.8 ± 7.8[a]	21.1 ± 8.1[a]	94.3 ± 59.3[a]	135.8 ± 68.4[a]	81.1 ± 28.5[a]
XYL	58 ± 76[a]	837 ± 1970[a]	943 ± 663[a]	77 ± 103[a]	195 ± 346[a]	1115 ± 1448[a]	33 ± 39[a]	126 ± 195[a]	346 ± 406[a]	2.8 ± 2.0[a]	2.2 ± 1.8[a]	3.0 ± 1.3[a]	9.6 ± 5.4[a]	18.8 ± 19.5[a]	46.4 ± 21.9[b#]	86.3 ± 40.4[a]	136.7 ± 79.5[a,b]	270.2 ± 186.9[b*#]
0	48 ± 47[a]	110 ± 126[a]	46 ± 19[a]	336 ± 652[a]	96 ± 122[a]	168 ± 195[a]	49 ± 53[a]	36 ± 42[a]	119 ± 72[b]	8.8 ± 16.7[a]	2.2 ± 2.1[a]	2.5 ± 2.9[a]	5.4 ± 3.4[a*]	7.4 ± 6.2[a]	13.5 ± 5.4[b]	79.8 ± 51.2[a]	85.6 ± 24.4[a]	81.6 ± 43.4[a]
5	92 ± 101[a]	244 ± 529[a]	410 ± 480[a]	755 ± 922[a]	643 ± 846[a]	856 ± 627[a]	147 ± 141[a]	63 ± 60[a]	202 ± 131[a]	7.4 ± 9.9[a]	10.6 ± 10.2[a*#]	5.0 ± 3.4[a]	14.5 ± 8.7[a]	14.4 ± 10.0[a]	27.3 ± 5.0[b]	79.6 ± 43.6[a]	92.3 ± 59.3[a]	106.1 ± 30.8[a]
10	109 ± 159[a]	335 ± 648[a]	673 ± 628[a]	270 ± 448[a]	440 ± 545[a,b]	918 ± 443[b]	164 ± 174[a]	98 ± 104[a]	209 ± 97[a]	2.1 ± 1.7[a]	6.0 ± 7.7[a]	4.3 ± 1.9[a]	17.7 ± 10.7[a]	15.8 ± 8.7[a]	31.8 ± 4.3[b]	62.6 ± 34.9[a]	66.3 ± 45.7[a]	114.0 ± 18.8[b]
20	282 ± 258[a]	463 ± 1051[a]	794 ± 989[a]	398 ± 364[a]	325 ± 359[a]	836 ± 616[a]	143 ± 136[a]	101 ± 70[a]	286 ± 130[b]	4.8 ± 4.3[a]	2.7 ± 2.0[a]	3.0 ± 1.9[a]	18.6 ± 6.4[a]	20.8 ± 7.9[a]	38.1 ± 9.1[b]	77.8 ± 29.4[a]	74.4 ± 52.6[a]	136.7 ± 68.9[a]
30	847 ± 1111[a]	598 ± 1020[a]	1547 ± 3023[a]	738 ± 751[a]	332 ± 493[a]	1003 ± 1069[a]	401 ± 299[a*#]	147 ± 134[a]	504 ± 538[a]	1.9 ± 1.1[a]	2.7 ± 3.1[a]	2.6 ± 1.4[a]	35.5 ± 19.8[a,b#]	22.7 ± 10.4[a]	43.9 ± 19.0[b#]	110.1 ± 67.8[a]	89.8 ± 56.2[a]	156.1 ± 125.9[a]
40	329 ± 630[a]	940 ± 1705[a]	710 ± 1093[a]	334 ± 441[a]	550 ± 669[a]	1121 ± 1724[a]	137 ± 160[a]	187 ± 148[a]	538 ± 678[a]	4.0 ± 3.5[a]	3.5 ± 2.9[a]	1.7 ± 0.6[a]	21.4 ± 20.6[a]	22.2 ± 14.8[a]	49.8 ± 31.9[a#]	96.5 ± 73.2[a]	99.5 ± 58.8[a]	130.1 ± 61.9[a]
50	175 ± 239[a]	743 ± 1241[a]	856 ± 1039[a]	398 ± 784[a]	610 ± 593[a]	1579 ± 2532[a]	120 ± 197[a]	239 ± 237[a]	683 ± 958[a]	2.2 ± 1.2[a]	3.1 ± 2.1[a]	2.2 ± 1.0[a]	15.0 ± 19.8[a]	27.7 ± 16.5[a,b#]	48.4 ± 37.2[b#]	63.2 ± 37.8[a]	149.8 ± 74.2[a]	170.6 ± 124.9[a]
60	945 ± 1533[a#]	457 ± 417[a]	1517 ± 1920[a]	615 ± 680[a]	442 ± 380[a]	1292 ± 1232[a]	224 ± 250[a]	258 ± 210[a#]	514 ± 612[a]	3.1 ± 1.4[a]	2.6 ± 1.7[a]	4.6 ± 3.6[a]	29.4 ± 25.2[a]	29.5 ± 13.8[a#]	52.0 ± 33.9[a*#]	121.2 ± 94.2[a]	122.0 ± 62.5[a]	182.8 ± 135.5[a]
75	471 ± 462[a]	634 ± 486[a]	1339 ± 1137[a]	789 ± 894[a]	738 ± 614[a]	1607 ± 1751[a]	308 ± 372[a]	368 ± 277[a*#]	363 ± 350[a]	3.2 ± 0.8[a]	2.8 ± 2.1[a]	2.5 ± 1.4[a]	32.5 ± 23.4[a#]	30.5 ± 16.8[a#]	58.4 ± 44.6[a*#]	118.3 ± 47.0[a]	144.5 ± 55.0[a]	201.2 ± 135.1[a]
90	637 ± 585[a]	520 ± 555[a]	786 ± 678[a]	685 ± 681[a]	645 ± 536[a]	513 ± 351[a]	202 ± 266[a]	292 ± 272[a#]	288 ± 228[a]	6.0 ± 3.2[a]	3.1 ± 1.9[a]	2.3 ± 0.9[a]	26.4 ± 22.8[a]	33.6 ± 19.9[a#]	40.3 ± 17.2[a]	113.8 ± 65.0[a]	117.7 ± 34.3[a]	129.2 ± 57.5[a]

B: base line. Anti-c: atropine, glycopyrrolate and saline. XYL: xylazine. VLF: very low frequency. LF: low frequency. HF: high frequency. LF/HF: low frequency/high frequency ratio. SD1: the standard deviation of poincare plot perpendicular to the line-of- identity SD2: the standard deviation of poincare plot to the line-of- identity A: Group atropine. G: Group glycopyrrolate. S: Group control. [ab]Means with different letters are statistically different among groups ($P < 0.05$). [*]Significantly different from base line values ($P < 0.05$). [#]Significantly different from 0 (after ketamine administration) ($P < 0.05$).

Table 3. Comparison of respiratory rate and SpO_2-R among groups after ketamine administration

Time	RR (breath/min)			SpO_2-R (bpm)		
(min)	A	G	S	A	G	S
5	18.0 ± 8.7[a]	15.7 ± 14.0[a]	20.1 ± 21.5[a]	125.4 ± 23.2[a]	125.4 ± 32.1[a]	118.0 ± 12.9[a]
10	15.0 ± 9.6[a]	13.2 ± 9.8[a]	40.8 ± 26.1[b]	118.8 ± 9.7[a]	126.1 ± 26.7[a]	101.2 ± 17.0[a]
15	9.0 ± 1.8[a]	16.0 ± 13.9[a]	42.8 ± 20.7[b]	100.4 ± 6.9[a]	106.0 ± 19.1[a]	93.2 ± 12.2[a]
20	18.6 ± 6.6[a]	20.8 ± 16.8[a]	43.1 ± 27.5[a]	102.4 ± 2.3[b]	103.1 ± 10.8[b]	89.4 ± 10.3[a]

RR: respiratory rate. SpO_2-R: oxygen saturation-pulse rate. A: Group atropine. G: Group glycopyrrolate. S: Group control. [ab]Means with different letters are statistically different among groups ($P < 0.05$).

Table 4. Comparison of the head up time, sternal recumbency time, walking time, maximum heart rate and peak time among groups after ketamine administration

Groups	HT (min)	ST (min)	WT (min)	max HR (beat)	PT (min)
A	33:04 ± 4:37[a]	37:10 ± 4:14[a]	33;59 ± 17:05[a]	206 ± 19[b]	1:16 ± 0:38[a]
G	30:33 ± 11:37[a]	33:23 ± 11:27[a]	38:00 ± 11:52[a]	185 ± 33[b]	1:17 ± 0:19[a]
S	32:44 ± 6:35[a]	38:45 ± 6:30[a]	43:07 ± 7:39[a]	130 ± 12[a]	1:23 ± 0:52[a]

A: Group atropine. G: Group glycopyrrolate. S: Group control. HT: head up time. ST: sternal recumbency time. WT: walking time. max HR: maximum heart rate. PT: peak time arrived to maximum heart rate. [ab]Means with different letters are statistically different among groups ($P < 0.05$).

atropine and glycopyrrolate on HRV in association with ketamine anesthesia. Our results show that the group which received glycopyrrolate, a non-centrally active anticholinergic, is at less risk of adverse cardiac events than subjects receiving atropine, a centrally active anticholinergic, when used in association with ketamine-xylazine anesthesia.

Ramamurthy *et al.* (10) and Mirakhur *et al.* (6) demonstrated that glycopyrrolate affects heart rate less than atropine, and several studies (1,11) demonstrated the minimal tachycardia is produced by glycopyrrolate, a quaternary ammonium compound that does not cross the blood-brain barrier.

Our study is consistent with that of Toft and Romer (15), who reported a significantly greater increase in heart rate following atropine administration than following the use of glycopyrrolate. There was only a significant increase of heart rate at 0 min in the glycopyrrolate group, while there were significant increases of heart rate at xylazine administration times of 0 and 5 min in the atropine group. Moreover, the heart rate of the atropine group reached a maximal level that exceeded that of the glycopyrrolate group. These results suggest that the parasympatholytic effect of atropine is stronger than that of glycopyrrolate.

Spectral analysis of heart rate variability is a powerful noninvasive method of quantifying drug effects on autonomic nervous system activity (7). In the time domain methods, which are the simplest ones calculated directly from the raw RR interval time series, SDNN and RMSSD reflect the complexity and safety of the heart (14). Our results show that SDNNs of atropine and glycopyrrolate group at 0 min significantly decreased, but that of the atropine group was significantly decreased only at 5 min. RMSSDs of the atropine and glycopyrrolate groups were significantly decrease from the time of xylazine administration to 20 min; the results obtained with pNN50 was similar to that of RMSSD. As these results are in agreement with Mirakhur *et al.* (6) and Salem *et al.* (12), who recommended that the lack of cholinomimetic effects of glycopyrrolate may be one explanation for the improved cardiovascular stability, we consider that atropine has a longer time of action and a stronger potency influenced on heart than glycopyrrolate, and the parasympathetic tone of atropine and glycopyrrolate were decreased from ketamine administration time to the awakening time.

In the frequency domain method, the commonly used parameters are the VLF, LF and HF component, and LF:HF ratio. The physiological explanation of the VLF component is much less defined and the existence of a specific physiological process attributable to these heart period changes might even be questioned. Thus VLF, which does not have coherent properties and which is affected by algorithms of baseline or trend removal, assessed from short-term recordings (≤ 5 min) is a dubious measure and should be avoided when interpreting the power spectral density of short-term ECGs (14). LF, which reflects a dynamic index of cardiac sympathetic tone and HF, and which in turn reflects a dynamic index of cardiac parasympathetic tone, is not fixed, but may vary in relation to changes in autonomic modulations of the heart period (7,14). Presently, the LF value of atropine group was not decreased, while that of glycopyrrolate group was decreased to a level comparable with its basal value. The HF values of both atropine and glycopyrrolate were significantly decreased to levels comparable with that

of the control group. However, glycopyrrolate had a longer time of action than atropine. Also, there were no differences in the LF:HF ratio among the experimental groups. However, the LF:HF ratios of atropine and glycopyrrolate increased to a level comparable with the control group. These results demonstrate that the cardiac autonomic balances of both atropine and glycopyrrolate are changed by the parasympatholytic effect, with glycopyrrolate displaying a less potent but longer lasting anticholinergic effect than atropine, which displayed a more potent and shorter lasting anticholinergic effect.

HRV contains nonlinear properties because of the complex regulatory control mechanisms. The Poincare plot is a simple and easily comprehendible nonlinear method. It is a graphical presentation of the correlation between consecutive RR intervals. SD1, which is mainly caused by respiratory sinus arrhythmia, describes short-term variability (parasympathetic tone). SD2 describes long-term variability (sympathetic tone) (4,16).

The SD1 values of atropine and glycopyrrolate were significantly decreased from xylazine, from the time of administration to 20 min to levels comparable with the control group, while the SD2 values were not significantly decreased. These results show that Poincare plot is strongly correlated with frequency domain component.

The values of respiratory rate and SpO_2-R were significantly decreased to compare with the value of control at 10, 15 and 20 min, in agreement with the HF results. Respiratory rate and SpO_2-R are related to HF, which are related to respiratory sinus arrhythmia, with HF being increased by bradypnea and bathypnea (8).

Moderate, but not statistically significant, correlations among parameters were evident with atropine and glycopyrrolate. However, statistical differences between atropine and glycopyrrolate were not showed. The correlations among parameters did not change when either atropine or glycopyrrolate were used in association with ketamine anesthesia, even when HRV was changed by atropine and glycopyrrolate administration.

We conclude that atropine used in association with ketamine anesthesia is less safe with the shorter time of action than glycopyrrolate used in association with ketamine, and that glycopyrrolate is preferable to atropine in association with ketamine anesthesia regarding cardiovascular stability.

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개에서 케타민-자일라진 마취동안 심박변이도에 대한 아트로핀과 글리코피롤레이트의 자율신경적 특성

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요 약 : 개의 마취에서 부작용을 예방하기 위하여 전마취제로 가장 일반적으로 사용되어지는 항콜린제는 심장에 부작용을 일으킬 수 있다. 비글견에서 케타민 마취 동안 심장의 교감신경과 부교감 신경의 균형에 대한 아트로핀과 글리코피롤레이트의 효과를 검증하기 위하여, 심박변이도, 마취 기간 그리고 행동 변화가 평가 되어졌다. 아트로핀과 글리코피롤레이트에서는 어떠한 일시적인 domain 차이도 없었다. 주파수 영역과 연관되어서는, 아트로핀과 글리코피롤레이트 효과는 모두 대조군에 비해 유의하게 낮게 나타났다 ($P < 0.05$). 그러나, 아트로핀의 RMSSD와 SD1은 기준선보다 낮았으며 ($P < 0.05$), 글리코피롤레이트의 LF:HF ratio는 기준선보다 높은 유의한 변화를 보였다 ($p < 0.05$). SD1의 변화는 주파수 도메인의 HF와 일치하는 변화를 보였으며 호흡수와 SpO_2-R의 변화와도 일치하는 변화를 보였다. 우리의 결과는 심장의 자율신경적 특성을 이용하여 글리코피롤레이트가 안전성과 작용 시간을 고려하여 개에서 케타민 마취시 항콜린제로 더욱 적당하다는 것을 증명한 것이다.

주요어 : 항콜린제, 심박변이도, 케타민, 교감신경, 자일라진