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Title page

The effects of anesthetic drug choice on heart rate variability and echocardiography parameters in cats

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Abstract

Heart rate variability (HRV) is one of the assessments of cardiovascular risk during general anesthesia. This study aimed to assess the effects of an anesthetic drug on HRV in cats and to provide information for clinical applications. Twenty-four healthy client-owned cats of various breeds, 12 females and 12 males scheduled for elective surgery, were enrolled in this study. The cats were premedicated and induced with 4 protocols: protocol 1, diazepam (0.3 mg/kg) and propofol (2-4 mg/kg); protocol 2, diazepam (0.3 mg/kg) and alfaxalone (1-3 mg/kg); protocol 3, diazepam (0.3 mg/kg) and ketamine (3-5 mg/kg); and protocol 4, xylazine (1 mg/kg) and tiletamine/zolazepam (Zoletil) (5 mg/kg). The heart rate and HRV of the 24 cats were collected before and at least 1 hour after administering the anesthetic drugs. Echocardiography was performed to evaluate heart function. Doppler was used to obtain the mean blood pressure. After anesthetic drug administration, higher heart rates were found in cats premedicated and induced with alfaxalone (p = 0.045) than in the other protocols. The lowest heart rate (HR) values were found in cats in protocol 4 using xylazine and Zoletil. The HRV low frequency (LF) and high frequency (HF) power ratios increased in all protocols except for cats premedicated and intubated with propofol. The standard deviation of the regular sinus beats (SDNN) was higher in cats premedicated and induced with ketamine than in other anesthetic protocols (p=0.015). An increase in sympathetic activity and reduced heart rate variability is associated with high blood pressure and left atrial dimension. The percentage of fractional shortening (FS) decreased in cats premedicated with ketamine. The results showed that the anesthesia method using diazepam and propofol was more effective in maintaining cardiovascular function than other anesthesia methods that were used in this study.

Keywords: anesthesia, cat, autonomic nervous activity

Introduction

Heart rate variability (HRV) has been suggested to be a noninvasive variable for use in autonomic nervous control[1]. Previous studies have reported the response of heart rate variability to many effects on medications in animals and used it as a predictor of mortality in cardiovascular conditions [2-6]. HRV includes two domains: the time domain and the frequency domain. Time domain parameters are measured from the R-R peak of the ECG, which can be calculated as SDNN (the standard deviation of the normal-to-normal R-R intervals). The frequency domain or spectral analysis is measured by transforming ECG signals into spectral signals. A previous study showed that the progression of cardiac conditions could alter cardiac autonomic activity, which leads to an increase in heart rate and a decrease in HRV [7,8].

The risk of cardiovascular complications is high in cats undergoing anesthesia. Anesthesia protocols have been developed to improve outcomes and provide safety for anesthesia in cat patients [9]. Propofol is a common anesthetic drug that has been used in dogs and cats [10]. However, respiratory depression and prolonged recovery are reported with propofol [11]. Alfaxalone is a sedative with a fast onset of effects that is commonly used for inducing short-term anesthesia in cats. The advantages of alfaxalone include muscle relaxation and rapid recovery [12]. Previous studies reported that alfaxalone had minimal cardiovascular effects [4, 13]. Alfaxalone is relatively safe and especially suitable for patients with heart disease, hypotension, and old age [14]. Ketamine is an effective drug for anesthetic induction in dogs and cats and is presumed to provide effects associated with an increased heart rate and can induce postoperative hyperthermia [15]. A combination of xylazine and Zoletil has been used as an ideal anesthetic agent in many animals, including cats, due to their reversible effects and low costs [16].

Concerning the various usages of anesthetic agents in cats, no studies have been performed to analyze cardiac autonomic activity using HRV to identify anesthetic agents that provide 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 and to provide information for clinical applications. HRV can be used to identify cats at high risk of hematological events and to indicate the need for cardiac monitoring after surgery. The results from this study could be used to indicate the presence of health problems, including heart conditions. We hypothesized that the minimal effects of anesthetic agents on the cardiovascular system in cats could be characterized by echocardiography combined with cardiac autonomic activity using heart rate and heart rate variability analysis.

Materials and methods

Animals

Twenty-four client-owned cats aged 2.6±0.4 years and weighing 3.4±0.2 kg who underwent the surgical procedure at Kasetsart University Veterinary Teaching Hospital Kamphaeng Saen were enrolled in this study. The study protocol was approved by the Institute Animal Care and Use Committee, Kasetsart University (ACKU-62-VET-059). All methods were carried out in accordance with university guidelines, the approved Animal Care and Use Committee, and the ARRIVE guidelines and regulations. The cat's owner was provided a consent form to approve the surgical procedure.

All cats were housed individually indoors throughout the study period. Cats were fasted 12 hours prior to the surgery and were randomly assigned into 4 groups of 4 anesthetic protocols and contained 6 cats in each protocol. Cats in protocol 1 were premedicated and induced with diazepam (0.3 mg/kg) and propofol (2-4 mg/kg). Cats in protocol 2 underwent anesthesia using diazepam (0.3 mg/kg) and alfaxalone (1-3 mg/kg). Diazepam (0.3 mg/kg) and ketamine (3-5 mg/kg) were used in protocol 3, and xylazine (1 mg/kg) and tiletamine/zolazepam (Zoletil) (5 mg/kg) were used in protocol 4. All drugs are administered intravenously according to the dose range by half, and the calculated dose is given rapidly (within 5-10 seconds). Then, an additional amount is given to produce the desired effect, except for xylazine and tiletamine/zolazepam (Zoletil), which is administered intramuscularly. Then, all cats were maintained under anesthesia for approximately 1 hour with a continuous infusion of 2% isoflurane with an oxygen flow rate of 1 L/min. The cats with the xylazine and tiletamine/zolazepam (Zoletil) protocol did not contain isoflurane to maintain anesthesia, and only oxygen was given throughout the period of anesthesia. The depth of anesthesia was according to stage 3 plane 2 in all cats, which is characterized by loss of consciousness, loss of pain sensation, and powers of coordinated movement. The eyeball becomes centrally located and motionless, decreases in depth, and increases in respiration rate, lachrymation, salivation, and muscle tone are diminished. All parameters were recorded continuously for further analysis using a blinded assessment.

Clinical evaluations

Routine laboratory evaluations were performed, including hematology and serum biochemistry analysis, as shown in Table 1. Cats with abnormal blood profile values were excluded from the study. The blood pressure measurement procedure during anesthesia is performed periodically every five minutes using an automatic noninvasive oscillometer cuff. Electrocardiograms were recorded to evaluate heart rate and heart rate variability. Transthoracic echocardiography was performed by a standard technique using a vivid 5 s machine with a 6 MHz probe. Parasternal long, short axis, and apical four-chamber views in the right and left parasternal positions were taken.

Echocardiographic images were captured and stored for offline analysis using a blinded assessment. Left ventricular wall structure and function were calculated by measuring the images from the two-dimensional plane (Figure 1).

HRV measurements

All cats underwent 3-channel 24-hour Holter ECG monitoring (BTL Medical Technologies, Thailand). Noninvasive cardiac autonomic nervous control measurements were performed on uploaded recordings by blinded assessment. Five electrodes were placed on the skin of the thorax with elastic tape to provide ECG recording for the baseline and 1 hour after administering anesthetic drugs. HRV analysis was performed according to a previously reported [17], and the baseline HRV was recorded on the day of surgery before the start of anesthesia and after the operation ended.

Heart rate variability (HRV) was analyzed for the time domain and the frequency domain, and time domain parameters were represented as the standard deviation of the RR interval or SDNN. The frequency domain parameters were measured using fast-Fourier transform analysis in two frequency bands: 0.15-0.5 Hz as a high frequency (HF) and 0.04-0.15 Hz as a low frequency (LF).

Statistical analysis

All data are shown as the mean ± standard error of the mean (mean ± SEM). The continuous variables and the differences between anesthetic protocols were analyzed using paired t tests and one-way ANOVA. A correlation matrix was used to represent the pair correlation of all the variables, and correlation coefficients were used to describe the association between variables and to analyze the multiple linear regression models that contained several independent variables. (GraphPad Prism

Software version 9.0, USA). A *p* value of 0.05 or less was considered statistically significant.

Results and Discussion

All 24 cats (age 2.6±0.4 years and weighing 3.4±0.2 kg) completed the study without any surgical complications. There were no significant differences among the groups concerning mean age, body weight, or duration of surgery (p=0.9641, p=0.9311, and p=0.9747, respectively). The results of blood profiles and cardiac function before the surgical procedure are summarized in Table 1 and Table 2, respectively. The blood profiles and echocardiographic parameters in all groups were within normal limits, and no significant differences among the groups were noted. The results from Table 2 showed that, the average of LA internal diameter before and after anesthesia was become dilation, in protocols 1, 2, and 4. However, in the anesthetic protocol 2, results showed that the LA mean values tended to be dilated than in the other protocols.

The heart rate decreased after the drug was administered in almost all groups except the protocol 2 group. Cats given protocol 4 had the lowest HR values (90±0.4 beats/min), and cats given protocol 2 had the highest HR (180.6±14.6), as shown in Table 3.

It has been demonstrated that hypotension during anesthesia may worsen patient outcomes [17]. The systolic blood pressure was significantly decreased in the protocol 4 group (p=0.03). However, those values were within normal limits. The standard deviation of the R-R interval (SDNN) increased after anesthetic drug administration in almost all groups except for protocol 2 (alfaxalone), indicating a reduction in parasympathetic tone, which was related to the significant increase in the heart rate in this group (Figure 2). LF was used as a marker of sympathetic activity [18]. The highest values of LF power were in the group of protocol 2, which indicated vagal inhibition.

The results from this study showed that diazepam and alfaxalone (protocol 2) produced an increase in heart rate and influenced sympathetic activity. Sympathetic activity is increased and correlated with the left atrium (LA) dimension. Left atrium enlargement is accepted as a result of pressure or volume overload and reflects systolic and diastolic dysfunction [19]. The relationship between LA enlargement and increased sympathetic activity has been shown in cats with anesthetic protocol 2. An enlargement of the LA and increased the filling pressure is thought to indirectly stimulate the cardiac autonomic system, including sympathetic and vagal nerve activities [20]. A previous study reported the correlation between left atrium dimensions and the risk of cardiovascular events. Assessment of LA size function, pulmonary veins and transmitral inflow are used to assess LV diastolic function [21].

The present study showed the correlation between echocardiography variables related to HR and HRV. The studies of cats given 4 anesthetic protocols demonstrated a correlation between left ventricle contractile function and LA and LV dimensions. In the present study, anesthetic protocol groups 3 and 4 had an increase in LV internal diameter when compared to anesthetic protocols 1 and 2. In cats given protocol 4, LA exhibited a strong negative correlation with fractional shortening and a weak positive correlation with the isovolumetric relaxation time (IVRT) (Figure 3). An increase in LA diameter leads to an increase in left atrial pressure, which promotes increased diastolic flow velocity in early diastole, thereby shortening the isovolumetric relaxation period. The results were similar to our expectations, and IVRT did not change with an increase in LA diameter. In addition, these left atrial diameter parameters exhibited weak positive correlations with the HRV time and frequency domains in all anesthetic protocols except anesthetic protocol 3 (Figure 3). These results suggested that the left atrium dimension might be used as an indicator to adjust the rate of fluid maintenance when using alfaxalone as an anesthesia drug to prevent pressure–volume overload and to preserve diastolic function as well as cardiovascular outcomes. In addition, a prolonged isovolumic relaxation time (IVRT), which is an early indicator of left ventricular diastolic dysfunction, showed the highest increase in anesthetic protocol 4 using xylazine combined with Zoletil, but it was preserved in anesthetic protocol 3 using ketamine. Ketamine may be useful as an anesthetic drug in cats with ventricular dysfunction. However, IVRT should be used to evaluate diastolic function in combination with other echocardiography variables, such as the transmitral inflow profile [21].

A previous study demonstrated that low LF⁄HF was an independent predictor of long-term mortality, cardiac events, and the risk of adverse events. Decreased LF⁄HF can be used as a predictor for hypotension or bradycardia. HRV may be used as a suitable tool to identify patients at high risk of a hemodynamic event [17]. In our study, the cats in protocol 1 had slightly reduced values of the LF/HF ratio and decreased percentage changes in heart rate variability when compared with other protocols. These results suggested that diazepam and propofol might preserve the cardiac autonomic activity balance better than the other anesthetic protocols. A marked HRV result for the time domain and frequency domain variation was observed in cats with anesthetic protocol 3 ($p<0.05$, $p<0.01$). These results indicated that the ability of the ECG Holter device to measure the time and frequency domains in cats was affected by the choice of anesthetic protocol. However, an insufficient number of cats in each group could affect the statistical analysis, which is a limitation of this study. Furthermore, only one set of ECGs was recorded for 1 hour, and recording for only a short period (1 hour) during a surgical protocol may affect the results. HRV analysis in anesthetized cats still requires further investigation to ensure its validity for use in future applications.

Conclusions

HRV can be used to identify cats at high risk of hematological events and to indicate the need for cardiac monitoring after surgery. The findings of this study could be used to indicate the presence of health problems, including heart conditions. Propofol could be used as a premedication and during intubation in cats since it had less effect on cardiovascular function than the other protocols. Results from this study suggested that diazepam (0.3 mg/kg) combined with propofol (2-4 mg/kg) should be used for premedication and intubation to provide cardiovascular stability in cats.

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Author contributions

All authors contributed the relevant work and approved the final manuscript. Study design and data analysis were conducted by S.P. Manuscript preparation was completed by S.P., C.P., and N.P.

Competing interest

All other authors have no relevant financial interests to be declared.

Data availability

All data generated or analyzed during this study are included in this published article, and the raw data are available in the supplemental files. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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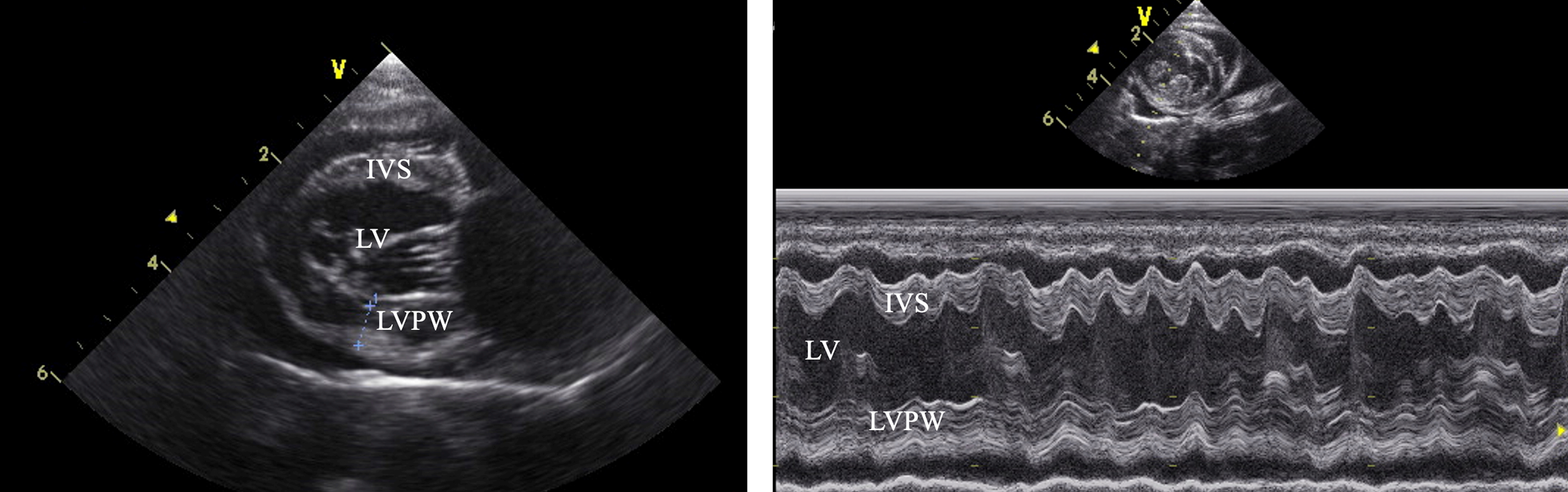
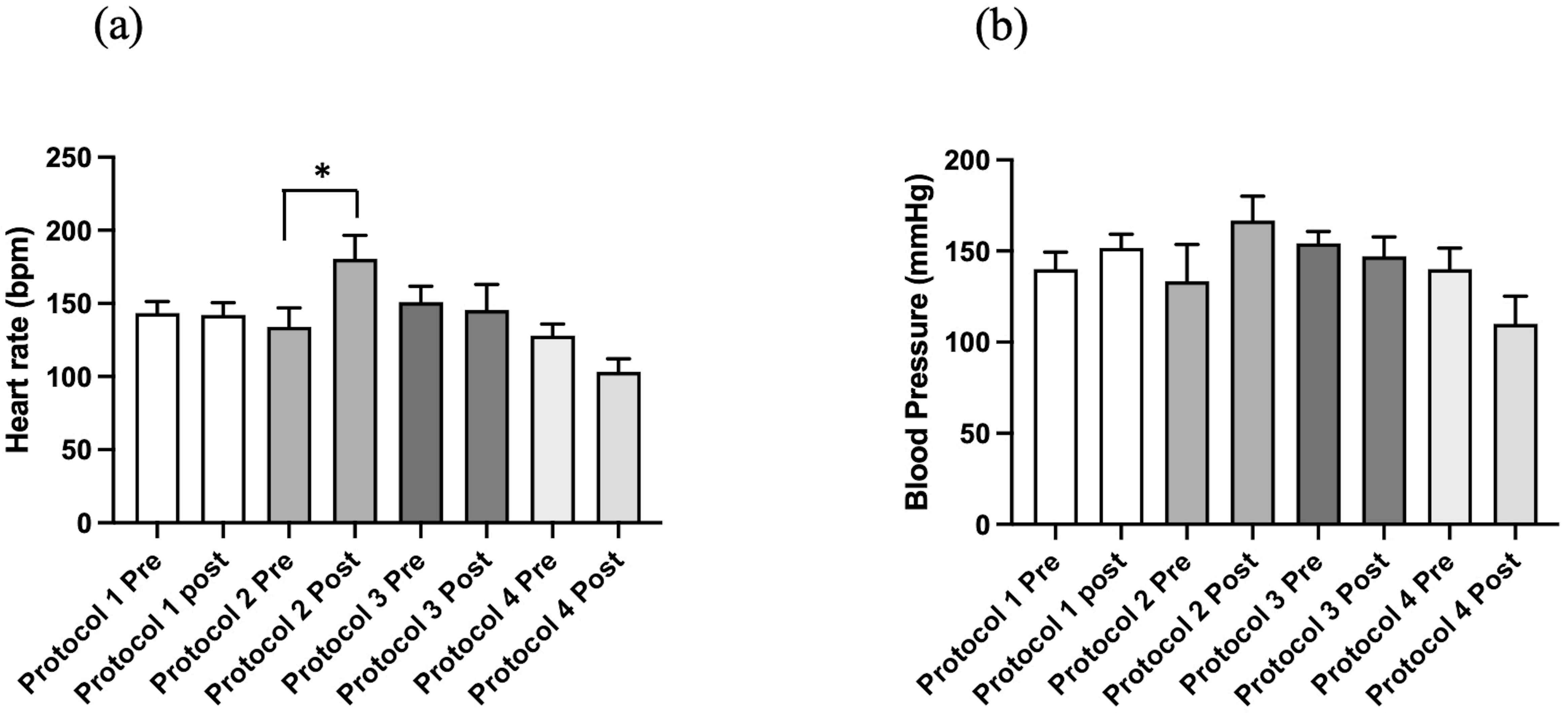
Figures

Figure 1. Echocardiographic of a transverse image of heart base (left) and M mode image of the left ventricle (right); IVS= interventricular septum thickness, LV = left ventricle, LVPW=left ventricular proximal wall thickness.

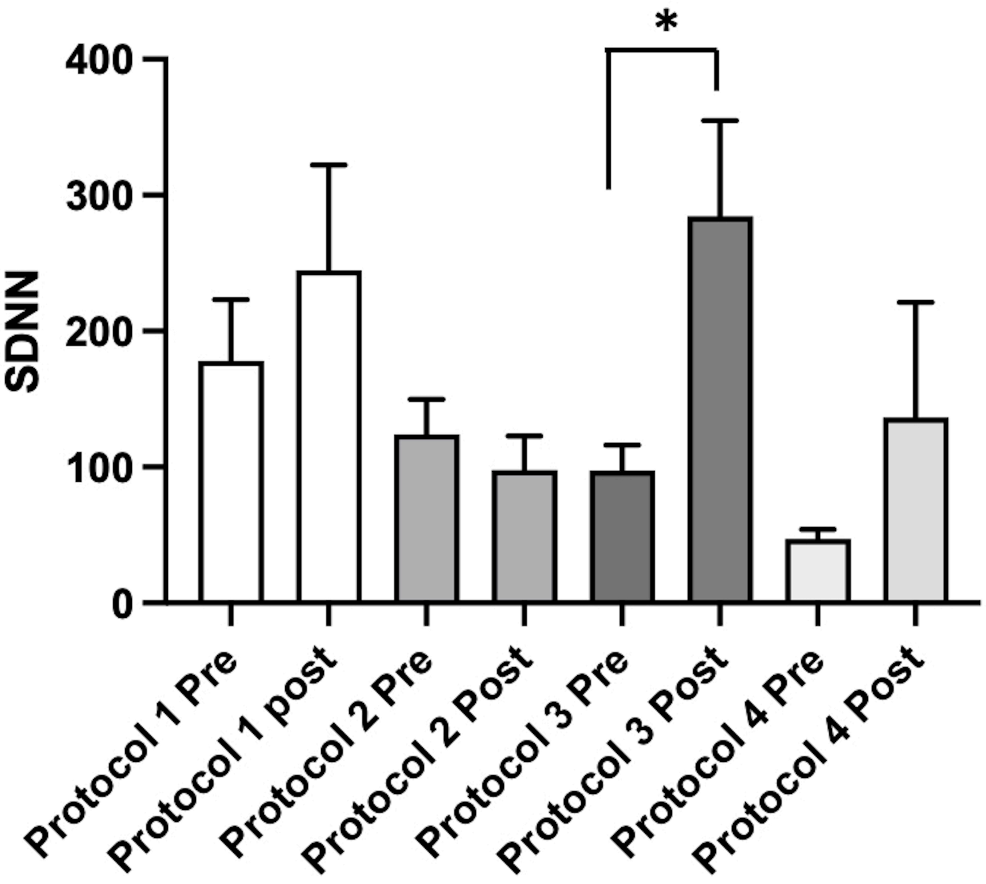
Figure 2. Effect of anesthetic drugs on heart rate (a), blood pressure (b), and heart rate variability (c) standard deviation of the R-R intervals (SDNN), (d) low frequency per high-frequency ratio (LF/HF). Values are expressed as the mean ± standard error of the mean (SEM). * Indicates $p<0.05$, ** indicates $p<0.01$. The *P value* summary for blood pressure was not significant in all protocols (*P value* summary = 0.1442, Protocol 1 pre vs. post, *P value* =0.3572, Protocol 2 pre vs. post, *P value* =0.2415, Protocol 3 pre vs. post, *P value* =0.5754, Protocol 4 pre vs. post, *P value* =0.1922).

Figure 3. Correlation matrix of all variables used in the cross-lagged models of cats in all anesthetic protocols. Protocol 1 (a), protocol 2 (b), protocol 3 (c), and protocol 4 (d). The color bar represents the correlation coefficients from −1 (red) to + 1 (blue). Blue squares represent significant positive correlations. Red squares represent significant negative correlations.


V
2
4
6
IVS
LV
LVPW
V
2
4
6
IVS
LV
LVPW

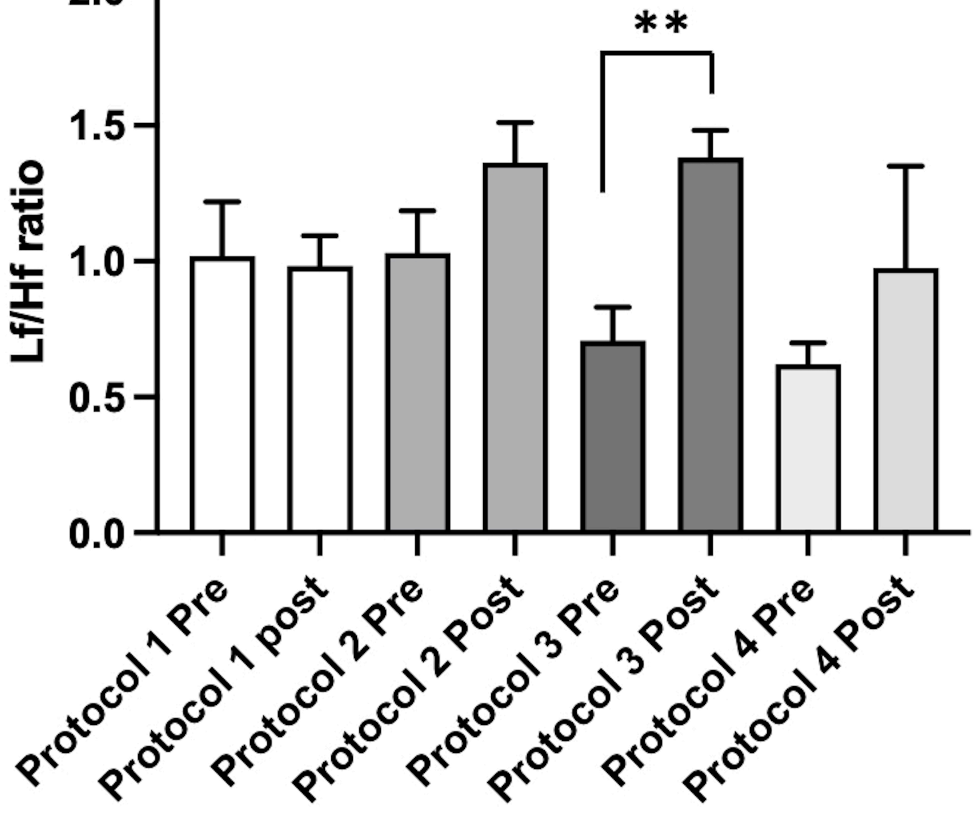

(a)
(b)
Heart rate (bpm)
250
200
150
100
50
0
*
Protocol 1 Pre
Protocol 1 post
Protocol 2 Pre
Protocol 2 Post
Protocol 3 Pre
Protocol 3 Post
Protocol 4 Pre
Protocol 4 Post
Blood Pressure (mmHg)
200
150
100
50
0
Protocol 1 Pre
Protocol 1 post
Protocol 2 Pre
Protocol 2 Post
Protocol 3 Pre
Protocol 3 Post
Protocol 4 Pre
Protocol 4 Post

(c)

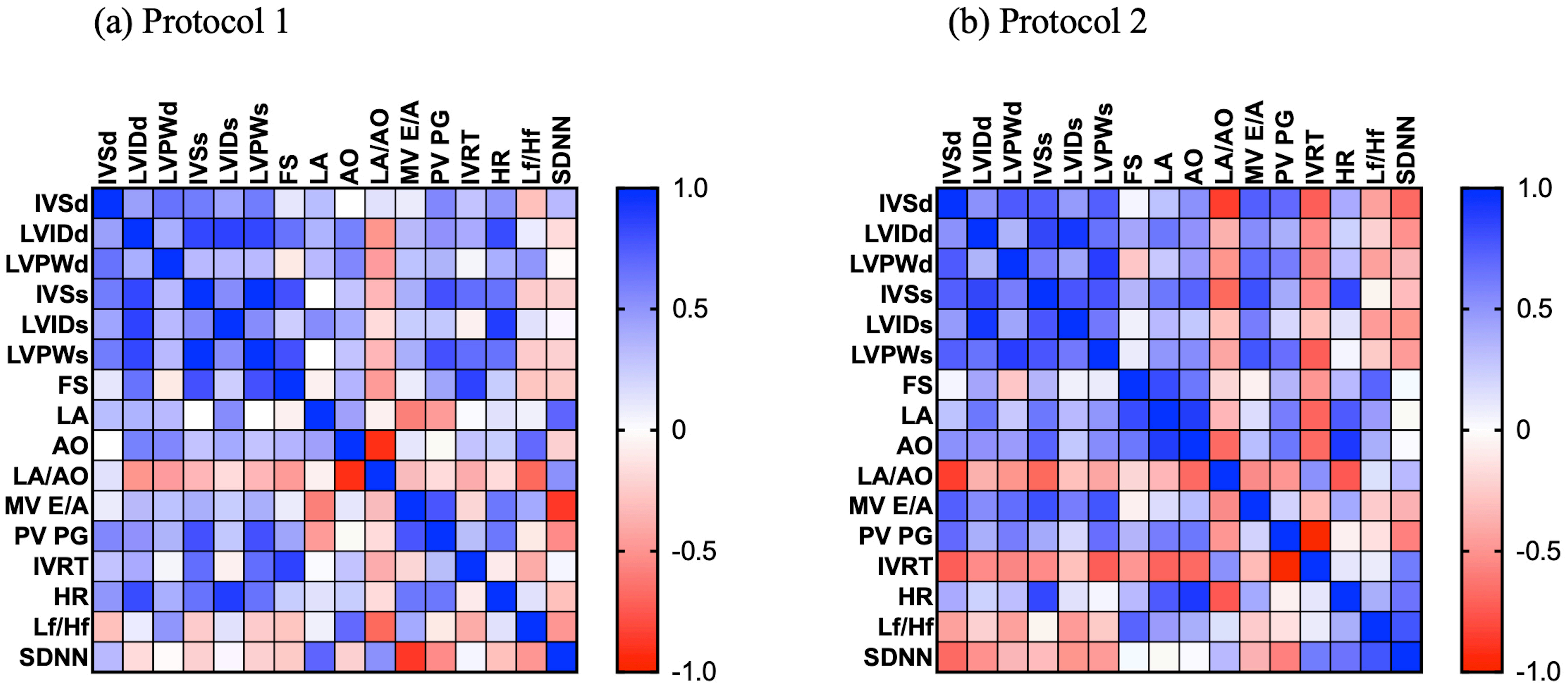


*
400
300
200
100
0
SDNN
Protocol 1 Pre
Protocol 1 post
Protocol 2 Pre
Protocol 2 Post
Protocol 3 Pre
Protocol 3 Post
Protocol 4 Pre
Protocol 4 Post

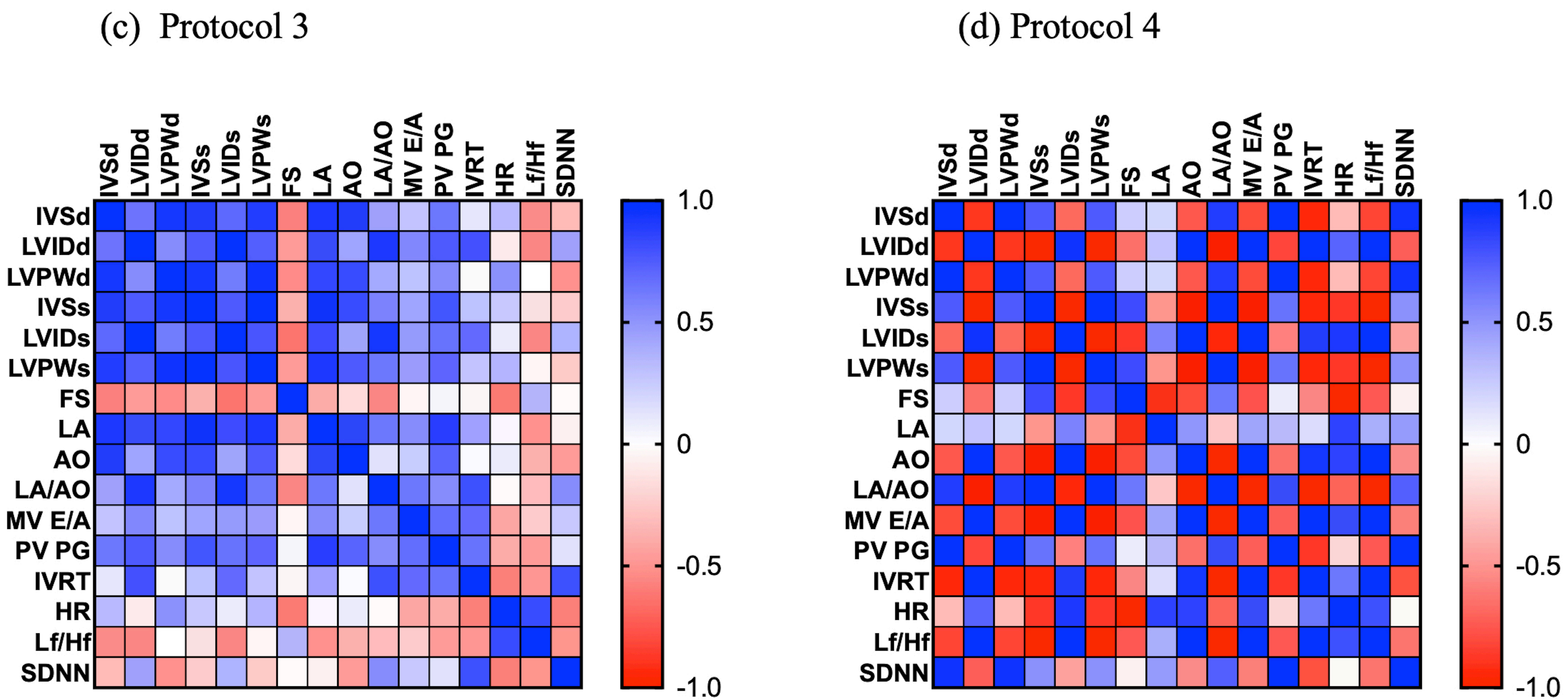
(d)



**
2.0
1.5
1.0
0.5
0.0
Lf/Hf ratio
Protocol 1 Pre
Protocol 1 post
Protocol 2 Pre
Protocol 2 Post
Protocol 3 Pre
Protocol 3 Post
Protocol 4 Pre
Protocol 4 Post



(a) Protocol 1
(b) Protocol 2
IVSd
LVIDd
LVPWd
IVSs
LVIDs
LVPWs
FS
LA
AO
LA/AO
MV E/A
PV PG
IVRT
HR
Lf/Hf
SDNN
1.0
0.5
0
-0.5
-1.0



(c) Protocol 3
(d) Protocol 4
IVSd
LVIDd
LVPWd
IVSs
LVIDs
LVPWs
FS
LA
AO
LA/AO
MV E/A
PV PG
IVRT
HR
Lf/Hf
SDNN
1.0
0.5
0
-0.5
-1.0

Table 1. A baseline of the blood profiles in four group protocols.

	Protocol 1 N=6	Protocol 2 N=6	Protocol 3 N=6	Protocol 4 N=6	Reference range
WBC ($x10^3$/ul)	17.76±1.69	17.58±3.57	20.47±1.56	17.80±1.75	5.5-19
RBC ($x10^6$/ul)	7.83±0.55	7.48±0.75	6.86±0.34	5.34±0.25	5-10
HGB (g/dL)	11.65±0.85	11.36±1.03	10.48±0.44	11.25±0.31	10-15
HCT (%)	33.15±2.61	33.46±2.44	32.25±1.23	32.54±1.29	30-45
PLT ($x10^3$/ul)	333.33±3.3	298.86±5.31	415.75±5.19	311.33±9.50	300-700
PROT (g %)	7.67±0.21	8.20±0.08	7.53±0.21	7.45±0.42	5.8-7.8
BUN (mg%)	21.43±2.89	25.68±1.05	20.00±3.05	18.20±3.85	15-34
Creatinine (mg%)	1.13±0.10	1.29±0.17	1.21±0.12	1.06±0.59	<2.0
ALT (IU/L)	76.40±2.18	46.60±4.66	43.0±1.33	29.0±0.11	28-76

Data are represented as the mean±SEM, WBC = White blood cell; RBC = Red blood cell; HGB = hemoglobin; HCT = hematocrit; PLT= Platelet; PROT= Total protein; ALT = Alanine aminotransferase.

Table 2 Echocardiographic parameters before and after surgery in the 4 protocols

Parameters		Protocol 1 N=6	Protocol 2 N=6	Protocol 3 N=6	Protocol 4 N=6
IVSd (cm)	Before	0.43±0.02	0.50±0.02	0.50±0.05	0.57±0.05
	After	0.43±0.02	0.56±0.04	0.52±0.05	0.53±0.05
LVIDd (cm)	Before	1.53±0.13	1.34±0.09	1.26±0.20	1.40±0.01
	After	1.35±0.14	1.33±0.09	1.42±0.17	1.40±0.01
LVPWd (cm)	Before	0.43±0.03	0.53±0.04	0.54±0.06	0.47±0.05
	After	0.42±0.04	0.53±0.05	0.53±0.04	0.53±0.06
IVSs (cm)	Before	0.55±0.02	0.59±0.05	0.60±0.06	0.63±0.06
	After	0.50±0.03	0.59±0.04	0.55±0.04	0.60±0.07
LVIDs (cm)	Before	0.95±0.09	0.77±0.04	0.80±0.14	0.80±0.04
	After	0.80±0.07	0.90±0.06	1.02±0.14	1.03±0.20
LVPWs (cm)	Before	0.53±0.02	0.57±0.04	0.56±0.06	0.63±0.02
	After	0.50±0.03	0.57±0.04	0.55±0.07	0.60±0.07
FS (%)	Before	38.0±3.65	42.0±1.31	38.0±2.31	44.6±2.72
	After	38.3±3.39	33.7±2.16	29.17±1.96	33.6±5.95
LA (cm)	Before	0.94±0.12	1.02±0.05	1.16±0.09	1.03±0.02
	After	1.02±0.13	1.17±0.03	1.10±0.07	1.07±0.02
LA/Ao Ratio	Before	1.41±0.03	1.57±0.07	1.40±0.06	1.53±0.06
	After	1.47±0.03	1.53±0.06	1.46±0.08	1.43±0.06
IVRT (mm)	Before	60.0±3.39	52.7±1.57	55.0±2.87	51.7±1.18
	After	62.2±3.24	58.0±4.95	55.3±2.85	70.3±7.04

Data are represented as the 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, FS = left ventricular fractional shortening, LA = left atrium, AO= aorta, LA/AO= left atrium diameter per aorta diameter ratio, IVRT = isovolumic relaxation time.

Table 3 Comparison of heart rate, heart rate variability, and blood pressure after anesthesia in 4 groups of protocols

	Protocol 1 N=6	Protocol 2 N=6	Protocol 3 N=6	Protocol 4 N=6
HR	142.2±8.3	180.6±14.6	145.5±17.5	90.0±6.9
SBP	151.7±7.6	165±12.3	138.3±7.03	110±10.8
SDNN	244.8±27.2	83.1±15.6	336.6±47.2	221.5±28.8
LF	1.85±0.7	3.39±1.2	2.23±0.9	2.84±1.6
HF	1.62±0.5	2.39±0.7	1.65±0.6	2.74±1.2
LF/HF	0.97±0.1	1.37±0.2	1.38±0.1	0.98±0.2

Data are represented as the mean ± SEM, HR = heart rate, SBP= systolic blood pressure, SDNN=standard deviation of the R-R intervals, LF = low frequency, HF= high-frequency, LF/HF= low frequency per high-frequency ratio.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- HRVanestheticcatsrawdata.xlsx