

## ORIGINAL ARTICLE

## Echocardiography Evaluation of Cardiac Performance in Cats Anesthetized by a Combination of Ketamine-Xylazine and Ketamine-Detomidine with Standard Incisions

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## ABSTRACT

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The heart is crucial in maintaining hemodynamic stability during anesthesia. The anesthetic combination of ketamine-xylazine is commonly used in cats, while the use of ketamine-detomidine is still limited and comparative data of their cardiovascular effect based on echocardiograph is still few. This research aims to evaluate the changes of physiological parameters and echocardiographs in cats anesthetized by the combination of ketamine-xylazine (KX) and ketamine-detomidine (KD) during a standard incision procedure. This parallel experimental study used 10 healthy male domestic cats aged 1.5–2 years and weighing 2–4 kg divided randomly into two treatment groups. Observation was conducted on 0, 30, and 60 minutes, measuring physiological parameters, left heart structure, stroke volume (SV), cardiac output (CO), ejection fraction (EF), and fractional shortening (FS). Data obtained were analyzed by two-way repeated measures ANOVA and the Bonferroni follow-up test. Results of this research showed that most echocardiography parameters are not significantly different based on time and treatment group. However, time factor significantly affects several physiological parameters and cardiac output (CO), while treatment group significantly affects EF and FS. Descriptively, the KD group showed lower EF and FS value compared to KX. In conclusion, KX and KD combination caused short-term physiological and cardiovascular changes in male domestic cat. The interpretation of this study is limited by the small number of samples and limited hemodynamic evaluation.

### Introduction

Heart is a vital organ important in maintaining the hemodynamics in animal. Heart function evaluation becomes a crucial aspect in veterinary medicine practice, especially in animals undergoing anesthesia and surgical procedures. One of the non-invasive methods commonly used to assess the structure and function of the heart in real time is echocardiography as it can give an objective image of cardiovascular changes during physiological condition or under anesthetics.<sup>1,2</sup> Thus, an understanding on the heart response in cats

during anesthetic procedure is important because anesthetics may influence the hemodynamic stability and cardiovascular function significantly.<sup>3,4</sup>

General anesthetic is commonly used to lower pain response, increase procedural safety, and ease patient handling.<sup>4,5</sup> However, anesthetics may cause changes in myocardial contractility, vascular tone, and cardiac output distribution which may disturb cardiovascular homeostasis.<sup>4,6</sup> Moreover, other complication such as cardiorespiratory depression and hypothermia may occur during anesthesia and potentially causes

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homeostasis imbalance in the animal.<sup>7</sup> For those reasons, suitable anesthetic combination is required to minimize negative impact on the cardiovascular system.

Ketamine is a dissociative anesthetic agent that has been widely used in veterinary clinical practice for over five decades. Its work mechanism involves its antagonism against N-methyl-D-aspartate (NMDA) receptor which inhibits pain transmission in the central nervous system.<sup>8</sup> In clinical use, ketamine is commonly combined with sedative agents or tranquilizer to improve the effectiveness of hemodynamic stability during anesthesia. One of the most common combinations to be used on small animals are ketamine-xylazine, in which xylazine is an agonist adrenergic  $\alpha_2$  receptor and as sedative, analgesic, and muscle relaxant effect.<sup>9</sup>

Other than xylazine, detomidine is also a part of  $\alpha_2$ -adrenergic agonist group which gives sedation, muscle relaxant, and analgesic effect through the stimulation of  $\alpha_2$  receptor in the central and peripheral nervous system.<sup>10</sup> Detomidine is known to have stronger sedative effect compared to several other  $\alpha_2$  agonist and has been used on various animals.<sup>11-14</sup> Although detomidine has been frequently evaluated in horses and large animals, echocardiography data showing cardiovascular response on ketamine-detomidine combination on cats are still limited. Thus, further evaluation on the cardiovascular effect of ketamine-detomidine combination in cats is still required.

Based on those reasons, this study is conducted to evaluate the changes in heart function on male domestic cat under anesthesia which used the combination of ketamine-xylazine and ketamine-detomidine through echocardiography observation during standard incision procedure. This research aims to analyze the difference in the short-term cardiovascular response between the two anesthetic combination groups. We hypothesize that the two anesthetic combinations caused changes in the heart cardiography parameter with different cardiovascular response between ketamine-xylazine and ketamine-detomidine.

## Materials and Methods

### Ethical Clearance

This study was conducted after being granted permission by the Ethical Committee for Animal Use in Research of the Faculty of Veterinary Medicine, Universitas Syiah Kuala, under the number No.449/KEPH/X/2025.

### Research and Test Animal Design

This research is a laboratory experimental study with parallel design conducted on ten male domestic cat aged 1.5-2 years weighing 2-4 kg. The cats were kept for 14

days acclimatization period before the treatment. During the period, all animal were given antiparasite ivermectin (Intermectin, PT. Tekad Mandiri Citra, Bandung, Indonesia) under 0,024 mg/kg BW dosage subcutaneously, combined antibiotic amoxycillin and clavulanic acid (Claneksi, Sanbe Farma, Bandung, Indonesia) under 10 mg/kg BW dosage orally once a day for five days along with B-complex vitamin administration (B-sanplex, Sanbe Farma, Bandung, Indonesia) under 0,25-0,5 ml/5-10 kg BW via intramuscular injection.

The cats were divided randomly into two treatment groups which consisted of five cats each. The groups are ketamine-xylazine (KX) group and ketamine-detomidine (KD) group. The number of animals in this research is used as a preliminary study to evaluate the cardiovascular response in cats against two anesthetic combinations.

### Anesthesia Procedure

Ten cats were fasted from eating for 8 hours and from drinking for 4 hours before the administration of anesthetics. Anesthesia was performed based on the treatment group: Group-I (G-I) ketamine-xylazine and Group-II (G-II) ketamine-detomidine. The anesthetics were administered via intramuscular injection (IM) on musculus semimembranosus by tubercle bacillus syringe 1 ml.<sup>15</sup> The dosage of the anesthetic combination for each group is presented in Table 1.

**Table 1.** The dosage of anesthetic combinations based on the treatment groups in cats.

| Treatment group | Drug combination      | Drug dosage           | Injection route |
|-----------------|-----------------------|-----------------------|-----------------|
| G-I             | Ketamine + Xylazine   | 10 mg/kg + 1 mg/kg    | IM              |
| G-II            | Ketamine + Detomidine | 10 mg/kg + 0.25 mg/kg | IM              |

### Standard Incision Procedures

Before the surgery, the flank area was shaved around 10 cm from the body median line on each side. After entering anesthesia phase, the cat was positioned in right lateral recumbency to ease the access to the surgical area. Surgical area was cleaned by physiological NaCl 0,9% liquid and disinfected by alcohol 70% and povidone iodine in a circular movement. A sterile drape is spread and fixed by towel clamp to maintain the sterile condition of the incision area.

Standard incision was made linear by the flank area 4 cm in length with depth reaching to stadium 3. The incision wound was then closed by simple interrupted pattern by using silk 3.0 USP thread (Silk Braided®, PT. Mega Pratama Medicalindo, Jakarta, Indonesia). In the last stage, the wound area was disinfected once more and closed by moist dressing.

## Echocardiograph Evaluation

Before the echocardiography was conducted, the left thoracic area was shaved to minimize hair interference in the ultrasonography wave transmission and to increase the imaging quality. Each cat's identity was inputted into the ultrasonography system before the observation. The cats were positioned in right parasternal (RPS) position as displayed in Figure 1. Ultrasonic gel was applied to the thoracic area to optimize the contact between the transducer and the skin surface during the observation.

Echocardiograph evaluation was performed in three observation period: the 0 minute (before anesthesia), the 30<sup>th</sup> minute (Sedation phase), and 60<sup>th</sup> minute (Recovery phase). The examination was performed with the transducer's short axis (SA) position in the 4<sup>th</sup> to 6<sup>th</sup> intercostal area after the heart beat location was identified. The imaging was conducted using brightness mode (B-mode) to visualize the heart structure and motion mode (M-mode) to measure the echocardiograph parameter.

The parameter for the left heart structure that were observed are: left ventricular internal dimension diastole (LVIDd), left ventricular internal dimension systole (LVIDs), left ventricular free wall diastole (LVWd), left ventricular free wall systole (LVWs), interventricular septum diastole (IVSd), and interventricular septum systole (IVSs). The heart blood output volume parameter consists of stroke volume and cardiac output (CO). The parameter for heart contraction strength consists of ejection fraction (EF) and fractional shortening (FS).<sup>16</sup> All echocardiograph imaging is stored and analyzed offline after all observation had finished.



**Figure 1.** The echocardiography examination position with the cat on right parasternal recumbency (Illustration).

## Statistical Analysis

The data of the study was analyzed by SPSS 25 for Mac software and presented in mean  $\pm$  standard deviation (SD) form. The echocardiography parameter differences based on treatment group and observation period was analyzed by two-way repeated measures analysis of

variance (two-way repeated measures ANOVA). Follow-up test pairwise comparison Bonferroni was conducted if significant changes was found. The  $p$  value  $<0.05$  shows significant difference.

## Results

### Physiological Parameter

The result of cat physiological parameter observation after the administration of anesthetic combination KX (G-I) and KD (G-II) is presented in Table 2. Statistical analysis shown that observation period effects significantly ( $p < 0.05$ ) the rectal temperature, pulse frequency, and breathing frequency.

The rectal temperature and pulse frequency did not show significant interaction with observation period and treatment groups ( $p > 0.05$ ), which means the two parameters are relatively similar in the two anesthetic groups. However, the breathing frequency shows significant interaction between observation period and treatment groups ( $p < 0.05$ ), which indicates different breathing frequency response in KX (G-I) and KD (G-II) during the observation period.

The rectal temperature in KX (G-I) and KD (G-II) shows gradual dropping trend from the minute 0 to 60. The pulse frequency shows a drop in minute 30 and remains lower compared to initial condition until minute 60. The breathing frequency also dropped on minute 30, then elevated again on minute 60. Bonferroni follow-up test resulted in significant difference between observation periods ( $p < 0.05$ ).

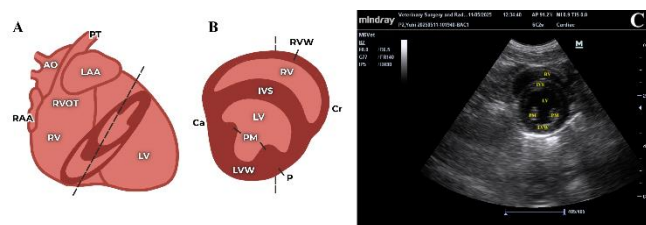
### Left Heart Structure

The parameter of left heart structure size in cats given anesthetic agents KX (G-I) and KD (G-II) was measured by ultrasonography equipment in brightness mode (B-mode) as shown in Figure 2A.

**Table 2.** The physiological parameter in cats being administered anesthetic agents KX (G-I) and KD (G-II) (Mean  $\pm$  SD).

| Observed parameter                        | Treatment group | Time interval (min)           |                              |                              |
|-------------------------------------------|-----------------|-------------------------------|------------------------------|------------------------------|
|                                           |                 | 0                             | 30                           | 60                           |
| Rectal temperature ( $^{\circ}\text{C}$ ) | G-I             | 38.1 $\pm$ 0.23 <sup>a</sup>  | 37.8 $\pm$ 0.31 <sup>b</sup> | 37.5 $\pm$ 0.36 <sup>c</sup> |
|                                           | G-II            | 37.9 $\pm$ 0.55 <sup>a</sup>  | 37.3 $\pm$ 0.78 <sup>b</sup> | 36.9 $\pm$ 0.89 <sup>c</sup> |
| Pulse frequency (times/min)               | G-I             | 123.0 $\pm$ 9.59 <sup>a</sup> | 81.6 $\pm$ 1.67 <sup>b</sup> | 84.0 $\pm$ 2.82 <sup>c</sup> |
|                                           | G-II            | 122.4 $\pm$ 22.3 <sup>a</sup> | 80.4 $\pm$ 2.96 <sup>b</sup> | 92.4 $\pm$ 7.53 <sup>c</sup> |
| Breathing frequency (times/min)           | G-I             | 41.2 $\pm$ 5.93 <sup>a</sup>  | 31.6 $\pm$ 2.96 <sup>b</sup> | 37.0 $\pm$ 4.24 <sup>c</sup> |
|                                           | G-II            | 49.2 $\pm$ 6.90 <sup>a</sup>  | 26.4 $\pm$ 6.54 <sup>b</sup> | 37.8 $\pm$ 3.03 <sup>c</sup> |

Different superscripts (<sup>a,b,c</sup>) on the same line indicates significant difference across observation time based on Bonferroni test ( $p < 0.05$ ).



**Figure 2.** A) The 2D illustration of heart structure with B-mode. B) The M-mode imaging position for accurate objective measurement of the size and function of LV in right parasternal short-axis view. C) The real time B-mode of cat heart echocardiography in right parasternal short-axis view.

The result of left ventricular internal dimension diastole phase (LVIDd) measurement in cats given the combination of KX (G-I) and KD (G-II) is shown in Table 3. Statistical analysis found that group, time or even the interaction between time and treatment group did not have significant effect ( $p > 0.05$ ). Descriptively, the changing pattern of LVIDd value shows fluctuate trend during the observation period. In KX and KD groups, the LVIDd dropped from minute 0 until minute 30 and elevated again up to minute 60. However, these changes are not statistically significant ( $p > 0.05$ ).

Statistical analysis shows that the size of left ventricular internal dimension in systole phase (LVIDs) in KX (G-I) and KD (G-II) is not significantly affected by treatment, time, or the interaction of time and treatment group ( $p < 0.05$ ). Descriptively, the pattern of changes in LVIDs size in KX (G-I) and KD (G-II) showed different response during observation period. KX (G-I) showed LVIDs size dropping from minute 0 to minute 60. Meanwhile, the KD (G-II) shows elevation in minute 30 and dropping again in minute 60. However, the Bonferroni follow-up test did not result in significant difference between observation periods ( $p > 0.05$ ), despite a difference was found between minute 30 and 60.

The size of left ventricular free wall in diastole phase (LVWd) in KX (G-I) and KD (G-II) showed that treatment groups, time, or interaction between time and treatment did not show significant difference ( $p > 0.05$ ). KX (G-I) showed elevated LVWd value in minute 30 then it dropped again on minute 60. However, KD (G-II) showed dropped LVWd value on minute 30 and remained stable until minute 60. Although the main analysis never showed significant effect from time, treatment, or the interaction of both ( $p > 0.05$ ), the Bonferroni follow-up test showed differences exist between minute 0 and minute 60 ( $p < 0.05$ ).

The size of left ventricular free wall in systole phase (LVWs) in KX (G-I) and KD (G-II) showed that time factor and the interaction between time and treatment shows significant changes ( $p < 0.05$ ). However, treatment group factor does not show significant difference between KX (G-I) and KD (G-II) ( $p > 0.05$ ). Descriptively, KX (G-I) shows elevated LVWs value on minute 30 and it dropped again on minute 60, closer to initial value. Meanwhile, KD

(G-II) shows relatively large drop of LVWs value on minute 30 and continues to drop until minute 60. Although the change pattern between the two groups differs during the observation period, Bonferroni follow-up test showed that the difference between observation periods is insignificant ( $p > 0.05$ ).

The size of interventricular septum in diastole phase (IVSd) in KX (G-I) and KD (G-II) shows that time factor has no significant effect ( $p > 0.05$ ). However, there is a significant interaction between time and treatment group, which means that IVSd changing pattern during the observation is different between KX and KD groups. Treatment factor also shows significant difference between KX (G-I) and KD (G-II) ( $p < 0.05$ ).

Descriptively, the KX (G-I) shows gradual elevation of IVSd value from minute 0 to minute 60. Meanwhile, KD (G-II) shows stable tendency on minute 30 and drops on minute 60. Although the difference in time is not statistically significant, the KD (G-II) has higher IVSd value compared to KX (G-I) during the observation period. The presence of significant interaction between time and treatment shows that the two anesthetic agents produced different changing pattern of interventricular septum in diastole phase during the observation period.

The size of interventricular septum in systole phase (IVSs) in KX (G-I) and KD (G-II) shows that the factors of treatment group, time, and interaction between time and

**Table 3.** The size parameter for left heart structure in cats being administered anesthetic agents KX (G-I) and KD (G-II) (Mean  $\pm$  SD).

| Observed parameter | Treatment group | Time interval (min)          |                              |                              |
|--------------------|-----------------|------------------------------|------------------------------|------------------------------|
|                    |                 | 0                            | 30                           | 60                           |
| LVIDd (mm)         | G-I             | 16.4 $\pm$ 3.36 <sup>a</sup> | 14.4 $\pm$ 2.80 <sup>a</sup> | 15.0 $\pm$ 2.12 <sup>a</sup> |
|                    | G-II            | 16.0 $\pm$ 1.43 <sup>a</sup> | 15.5 $\pm$ 0.96 <sup>a</sup> | 17.2 $\pm$ 1.31 <sup>a</sup> |
| LVIDs (mm)         | G-I             | 6.4 $\pm$ 1.70 <sup>a</sup>  | 5.8 $\pm$ 1.33 <sup>a</sup>  | 5.8 $\pm$ 1.57 <sup>a</sup>  |
|                    | G-II            | 9.1 $\pm$ 1.27 <sup>a</sup>  | 13.4 $\pm$ 1.82 <sup>a</sup> | 11.7 $\pm$ 0.61 <sup>a</sup> |
| LVWd (mm)          | G-I             | 6.0 $\pm$ 0.40 <sup>a</sup>  | 8.8 $\pm$ 0.63 <sup>ab</sup> | 5.5 $\pm$ 0.65 <sup>b</sup>  |
|                    | G-II            | 12.1 $\pm$ 1.44 <sup>a</sup> | 9.3 $\pm$ 8.25 <sup>ab</sup> | 9.3 $\pm$ 3.24 <sup>b</sup>  |
| LVWs (mm)          | G-I             | 6.2 $\pm$ 0.29 <sup>a</sup>  | 7.4 $\pm$ 1.77 <sup>a</sup>  | 6.2 $\pm$ 0.73 <sup>a</sup>  |
|                    | G-II            | 14.0 $\pm$ 1.02 <sup>a</sup> | 8.1 $\pm$ 7.70 <sup>a</sup>  | 7.0 $\pm$ 5.28 <sup>a</sup>  |
| IVSd (mm)          | G-I             | 5.1 $\pm$ 0.58 <sup>a</sup>  | 5.4 $\pm$ 1.48 <sup>a</sup>  | 6.6 $\pm$ 0.70 <sup>a</sup>  |
|                    | G-II            | 8.2 $\pm$ 1.15 <sup>a</sup>  | 8.3 $\pm$ 1.67 <sup>a</sup>  | 6.8 $\pm$ 1.54 <sup>a</sup>  |
| IVSs (mm)          | G-I             | 7.4 $\pm$ 2.12 <sup>a</sup>  | 5.7 $\pm$ 2.71 <sup>a</sup>  | 6.2 $\pm$ 0.90 <sup>a</sup>  |
|                    | G-II            | 8.4 $\pm$ 1.51 <sup>a</sup>  | 7.6 $\pm$ 2.28 <sup>a</sup>  | 6.6 $\pm$ 0.96 <sup>a</sup>  |

Different superscripts (<sup>a,b,c</sup>) on the same line indicates significant difference across observation time based on Bonferroni test ( $p < 0.05$ ).

treatment group do not show significant effect ( $p > 0.05$ ). Descriptively, the KX (G-I) shows dropping IVSs values on minute 30 and elevating again on minute 60. Meanwhile, KD (G-II) shows gradual drop of IVSs value during the observation period. However, the changes do not give statistically significant difference between time or treatment groups.

### Cardiac Blood Flow Parameter

The result of stroke volume (SV) and cardiac output (CO) observation in cats administered ketamine-xylazine (KX) and ketamine-detomidine (KD) during the observation period is presented in Table 4. The SV value in KX group tends to drop from minute 0 to minute 60, while in KD (G-II) it underwent a drop in minute 30 and elevation in minute 60. However, the statistical analysis shows that the factor of time, treatment, or interaction between time and treatment has no significant effect ( $p > 0.05$ ).

The CO value in the two treatment groups KX and KD shows a drop in minute 30 compared to minute 0 and then elevation in minute 60. The analysis resulted in the factor of treatment and interaction between time and treatment not showing significant effect ( $p > 0.05$ ). However, time factor shows significant difference against CO value ( $p < 0.05$ ). The Bonferroni follow up test shows that there is a significant difference between minute 0 and minute 30 ( $p < 0.05$ ), but there is no significant difference in minute 60 against minute 0 and 30 ( $p > 0.05$ ).

**Table 4.** The parameter of heart blood flow volume in cats administered anesthetic agents KX (G-I) and KD (G-II) (Mean  $\pm$  SD).

| Observed parameter      | Treatment group | Time interval (min)          |                              |                              |
|-------------------------|-----------------|------------------------------|------------------------------|------------------------------|
|                         |                 | 0                            | 30                           | 60                           |
| Stroke volume (ml)      | G-I             | 5.84 $\pm$ 3.97 <sup>a</sup> | 4.95 $\pm$ 3.47 <sup>a</sup> | 4.47 $\pm$ 2.09 <sup>a</sup> |
|                         | G-II            | 5.90 $\pm$ 1.10 <sup>a</sup> | 4.54 $\pm$ 0.43 <sup>a</sup> | 5.92 $\pm$ 1.19 <sup>a</sup> |
| Cardiac output (ml/min) | G-I             | 786 $\pm$ 482 <sup>a</sup>   | 420 $\pm$ 289 <sup>b</sup>   | 447 $\pm$ 151 <sup>ab</sup>  |
|                         | G-II            | 729 $\pm$ 24.0 <sup>a</sup>  | 372 $\pm$ 31.5 <sup>b</sup>  | 612 $\pm$ 128 <sup>ab</sup>  |

Different superscripts (<sup>a,b,c</sup>) on the same line indicates significant difference across observation time based on Bonferroni test ( $p < 0.05$ ).

### Cardiac Contraction Parameter

The result of cardiac contraction power observation in cats given anesthetic combinations of KX (G-I) and KD (G-II) is presented in Table 5. Statistical analysis showed that treatment groups have significant effect on ejection fraction (EF) and fractional shortening (FS) values ( $p < 0.05$ ). However, the factor of time and interaction between observation period and treatment groups does not show significant effect ( $p > 0.05$ ).

The FS parameter in KX (G-I) shows decreasing pattern in minute 30 and continued to elevation on

minute 60. Meanwhile, KD (G-II) shows decrease in minute 30 and tend to remain low until minute 60. The Bonferroni follow up test shows that there is no significant difference between observation period in parameter EF and FS ( $p > 0.05$ ).

**Table 5.** The parameter for hearth contraction strength in cats administered anesthetic agents KX (G-I) and KD (G-II) (Mean  $\pm$  SD).

| Observed parameter        | Treatment group | Time interval (min)          |                              |                              |
|---------------------------|-----------------|------------------------------|------------------------------|------------------------------|
|                           |                 | 0                            | 30                           | 60                           |
| Ejection fraction (%)     | G-I             | 85.6 $\pm$ 5.50 <sup>a</sup> | 83.1 $\pm$ 10.1 <sup>a</sup> | 87.3 $\pm$ 4.12 <sup>a</sup> |
|                           | G-II            | 78.5 $\pm$ 6.66 <sup>a</sup> | 67.7 $\pm$ 6.06 <sup>a</sup> | 69.0 $\pm$ 3.01 <sup>a</sup> |
| Fractional shortening (%) | G-I             | 55.0 $\pm$ 7.12 <sup>a</sup> | 50.7 $\pm$ 13.1 <sup>a</sup> | 56.6 $\pm$ 4.31 <sup>a</sup> |
|                           | G-II            | 47.4 $\pm$ 7.62 <sup>a</sup> | 34.7 $\pm$ 4.11 <sup>a</sup> | 34.0 $\pm$ 1.89 <sup>a</sup> |

Different superscripts (<sup>a,b,c</sup>) on the same line indicates significant difference across observation time based on Bonferroni test ( $p < 0.05$ ).

### Discussion

Physiological parameter such as temperature, pulse frequency, and breathing frequency are important indicators to note during observation to understand the animal's health status in physiological and pathological condition.<sup>17</sup> The drop of rectal temperature occurring in groups during anesthesia may be related to the depression of thermoregulator center and the redistribution of body heat due to peripheral vasodilatation that is triggered by the anesthetic agents.<sup>18</sup> Although rectal temperature drop occurred in both groups, the body temperature value was still within normal cat physiologic value, except in KD (G-II) on minute 60, which shows a drop under normal range. The normal rectal temperature value in cat is within 36.7–38.9 °C.<sup>19</sup>

The drop of body temperature in KD (G-II) may be related to the effect of agonist  $\alpha$ 2-adrenergic from detomidine which is known to give effects like sedation, hypothermia, and sympathetic nerve activity drop.<sup>20,21</sup> Mild hypothermia often occurs during anesthesia and surgery. Body temperature changes during anesthesia also may be influenced by environmental factor and the duration of the surgical procedure.<sup>22</sup>

Normal heartbeat frequency in adult cat is 140 to 240 beats per minute (averaging at 195)<sup>23</sup> and the normal cat breathing frequency ranges at 20–40 breaths per minute.<sup>24</sup> The pulse frequency and breathing frequency in both groups decreased on minute 30 after anesthesia. This is in line with the effect of agonist  $\alpha$ 2-adrenergic which can lower sympathetic activities through norepinephrine release that further causes bradycardia and decrease in respiration frequency.<sup>25</sup> Ketamine is known to have stimulatory effect on cardiovascular system in the form of increasing heart rate and heart

output.<sup>26,27</sup> However, that effect can be modulated by combining with sedative agents such as xylazine or detomidine.<sup>28</sup> In this research, the pulse frequency shows relatively similar changing pattern between the two groups, while the breathing frequency shows significant interaction between time and treatment. This indicates that there is a difference in respiratory response in the combinations KX (G-I) and KD (G-II) during the observation period.

The evaluation of left ventricle function through echocardiography examination is a non-invasive method commonly used to assess the changes in heart structure and function during anesthesia.<sup>29</sup> The parameter left ventricular internal dimension diastole (LVIDd) in this study fluctuated within normal range and shows no significant changes for left ventricular dimension in diastole phase during the observation period. The average value of LVID in diastole phase ranges between 11.22–17.54 mm.<sup>30,31</sup>

The left ventricular internal dimension systole (LVIDs) shows decreasing LVIDs value to under the normal range during the observation in KX group. The normal range of LVIDs value ranges in 6.03-9.41 mm.<sup>30,31</sup> In domestic home cats average LVIDd value of 0.78 cm and LVIDs value of 1.48 cm are also reported.<sup>32</sup> However, KD group underwent an increase in minute 30 before a decrease again in minute 60. The increase of LVIDs size may indicate the lowering of ventricle contractile ability during systole phase, although the changes between the time period in this research is not significantly different.

The left ventricular free wall diastole (LVWd) and left ventricular free wall systole (LVWs) parameters show different changing pattern among the treatment groups during the observation period. In the systole phase, the ventricle contracted so the ventricle wall appears thicker and the ventricle diameter smaller. On the other hand, during diastole phase, ventricle relaxes and the blood fills the atrium.<sup>33</sup> The size changes of LVWd and LVWs in this research may be related to the changes of myocardium contractility during anesthesia, although most changes do not show significant statistical changes between observation time. The normal value for LVWd ranges at 3,54-5,85 mm and for LVWs at 5,05-7,58 mm.<sup>31</sup> Based on this study, the LVWs size is larger than the normal size of LVWs in KD (G-II) on minute 0 and minute 30. According to Noviana and Kurniawan (2013), the LVW size in domestic cat is thicker during systole compared to diastole.<sup>32</sup> The size of LVW will increase during systole because the heart will contract to pump blood all over the body.<sup>33</sup>

According to Kayar *et al.* (2014), the normal value of IVSd ranges at IVSd 1.57-5.46 mm.<sup>31</sup> The value of interventricular septum diastole (IVSd) shows significant interaction between time and treatment. This indicates

that both anesthetic combinations resulted in different pattern of interventricular septum change during the observation. KD (G-II) has relatively high IVSd value compared to KX during the observation period. The normal IVSs size is ranges at 3,91-7,58 mm.<sup>31</sup> In cats given KX (G-I) and KD (G-II) anesthetic agents, the IVSs values drop on every observation period, on minute 30 and minute 60 which are not significantly different. However, the IVS size at systole in KD (G-II) on minute 0 and minute 30 are above the normal range. According to Noviana and Kurniawan (2013), local cat IVS size is thicker during systole compared to diastole,<sup>32</sup> because during systole the heart is filled with blood which makes the heart wall relaxed and turn thinner.<sup>34</sup> However, the interventricular septum systole (IVSs) shows no significant differences between time or even between treatment groups.

The stroke volume (SV) and cardiac output (CO) are used to evaluate the heart's ability to pump blood during anesthesia.<sup>35</sup> Factors influencing the amount of blood pumped by the heart are the size of the ventricle and the cardiac strength during pumping.<sup>35</sup> Based on this study, the SV values show no significant difference against time, treatment or the interaction between the two. The SV value in KD (G-II) elevated on minute 60. Heart muscle enlargement will increase the blood volume, so the heart can contain more blood (diastole phase) and the SV during rest will be larger. This allows the blood to pump blood in the same amount every minute with lower heartbeat frequency.<sup>35</sup> However, the stroke volume change pattern in the two anesthetic agents group KX (G-I) and KD (G-II) fluctuated within the normal range. The normal SV value in domestic house cat is reported to range at 3.42 – 5.97 ml and averaging at 4.88 ml.<sup>32</sup>

Cardiac output (CO) is the volume of blood pumped by the heart in one minute.<sup>36</sup> CO measurement in anesthetized cat is used to characterized the hemodynamic effect of a drug or a drug combination.<sup>37</sup> The CO value of the two groups decreased in minute 30 and increased again in minute 60, although they show insignificant difference. The normal CO value ranges at 659.13 – 1185.27 ml/minute with an average of 865,18 ml/minute.<sup>32</sup> The CO value changes during anesthesia may be related to the anesthetic combination affect to the heartbeat, preload, and myocardium contractility.<sup>36</sup> The surgery and anesthesia can influence cardiovascular function through the changes in vascular tonus, hypothermia, and light myocardium depression during the procedure.<sup>38</sup> Anesthetic agents used to sedate rodents are known to affect HR myocardium contractility, preload, and afterload.<sup>39</sup>

The parameters ejection fraction (EF) and fractional shortening (FS) are used to evaluate the left ventricle contraction function during systole phase.<sup>40</sup> In this study, treatment groups show significant effect against EF and

FS value, while time and the interaction between time and treatment has no significant effect. However, KD (G-II) shows lower EF and FS values compared to KX (G-I) during the observation period. The drop in EF and FS values may illustrate the lowering left ventricle contractility function,<sup>41</sup> although the value obtained during this study is still within the normal physiological range for cats. The normal FS value in cats ranges at 29-55% or 45-55% and can increase or decrease when given anesthetic agent.<sup>40,42</sup> The average normal FS value in domestic house cat is 47.81 % and the average EF value is 82.28%.<sup>32</sup> The EF value of KD (G-II) fluctuated and tend to be below the normal average value during the observation. The lower the EF value, the more significant the drop in systole function.<sup>41</sup> Systolic dysfunction is also called heart contractility disturbance which causes the decrease of EF left ventricle and heart's inability to provide enough blood supply required for tissue perfusion.<sup>43</sup>

In conclusion, the anesthetic combination of ketamine-xylazine (KX) and ketamine-detomidine (KD) in healthy male domestic cats caused changes in physiological parameters and echocardiograph for 60 minutes. Most of the parameters did not show significant difference between groups or time. The cardiac output (CO), ejection fraction (EF), and fractional shortening (FS) show variations related to time and/or treatment, with the tendency of lower value in KD (G-II). In general, the two protocols resulted in relatively similar short-term cardiovascular response within the condition of this study.

The study is limited by the relatively small sample size, the short observation duration, and the lack of follow up hemodynamic parameter evaluation. Thus, a follow up study with larger sample size and more comprehensive hemodynamic evaluation is required.

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## Conflict of Interest

There is no conflict of interest to be reported.

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