

ELECTROCARDIOGRAM OF PIGS (*Sus scrofa*) ANESTHETIZED WITH A COMBINATION OF KETAMINE-MEDETOMIDINE AND KETAMINE-ACEPROMAZINE

Jessica Anggun Safitri^{1*}, Gunanti², Deni Noviana², and Sus Derthi Widhyari²

¹Postgraduate Program in Animal Biomedical Sciences, Department of Pathology and Reproductive Clinics, Faculty of Veterinary Medicine, IPB University, Bogor, Indonesia

²Department of Pathology and Reproduction Clinic, Faculty of Veterinary Medicine, IPB University, Bogor, Indonesia

*Corresponding author: jessica_anggun@apps.ipb.ac.id

ABSTRACT

This study aims to evaluate and compare the effects of the combination of ketamine-medetomidine and ketamine-acepromazine anesthesia on pig electrocardiogram (ECG) images. The study was conducted to see the ECG Leads II in six pigs which were divided into two groups. Group I (K1) was given a combination of ketamine (10 mg/kg BW) and medetomidine (0.08 mg/kg BW), while Group II (K2) was given a combination of ketamine (22 mg/kg BW) and acepromazine (1.1 mg/kg BW) intramuscularly. ECG recording was performed after the pigs were anesthetized at the surgical stage by attaching the recording electrodes to the front wall of the chest, front left and right ankles, and back right and left back ankles. The ECG recording used 1 voltage (1 cm = 1 mV) with a speed of 25 mm/sec. The parameters observed were heart rate frequency, heart rhythm, P duration, P amplitude, PR interval, R amplitude, QRS interval, QT interval, ST segment, T wave, and Mean Electrical Axis (MEA). Data obtained from this study were analyzed by T-test. The results showed that K1 had an average heart rate of 100 x/minute, regular heart rhythm, P duration of 0.07 sec, P amplitude of 0.27 mV, PR interval of 0.17 sec, R amplitude of 0.75 mV, QRS interval of 0.05 sec, QT interval of 0.20 sec, ST segment of 0.17sec, T wave of 0.17 mV, and MEA of 83.60°; meanwhile, K2 had an average heart rate of 122 x/minute, regular heart rhythm, P duration of 0.06 mm/sec, P amplitude of 0.23 mV, PR interval of 0.14 sec, R amplitude of 0.80 mV, QRS interval of 0.04 sec, QT interval of 0.16 sec, ST segment of 0.14 sec, T wave of 0.12 mV, and MEA of 68.60. The ketamine-medetomidine combination produced good quality of anesthetics for the cardiovascular system.

Key words: acepromazine, electrocardiogram, ketamine, medetomidine, pig

ABSTRAK

Penelitian ini bertujuan mengevaluasi dan membandingkan efek kombinasi anestesi ketamin-medetomidin dan ketamin-acepromazin terhadap gambaran elektrokardiogram (EKG) babi. Penelitian dilakukan untuk melihat gambaran EKG sadapan II pada 6 ekor babi dibagi ke dalam dua kelompok. Kelompok I (K1) diberi kombinasi anestesi ketamin dosis 10 mg/kg bobot badan medetomidin dosis 0.08 mg/kg bobot badan dan kelompok II (K2) ketamin dosis 22 mg/kg bobot badan acepromazin dosis 1,1 mg/kg bobot badan secara intramuskulus. Perekaman EKG dilakukan setelah babi teranestesi pada stadium pembedahan dengan memasang elektrode perekam pada dinding depan dada, pergelangan kaki kanan dan kiri depan serta pergelangan kaki kanan dan kiri belakang. Perekaman EKG menggunakan voltase 1 (1 cm = 1 mV) dan kecepatan perekaman 25 mm/detik. Parameter yang diamati adalah frekuensi denyut jantung, ritme jantung, durasi P, amplitudo P, interval PR, amplitudo R, interval QRS, interval QT, segmen ST, gelombang T dan Mean Electrical Axis (MEA). Data yang diperoleh dari hasil penelitian ini dianalisis dengan T-test. Hasil penelitian diperoleh rata-rata pada K1 frekuensi denyut jantung 100 x/menit, ritme jantung reguler, durasi P 0,07 detik, amplitudo P 0,27 mV, interval PR 0,17 detik, amplitudo R 0,75 mV, interval QRS 0,05 detik, interval QT 0,20 detik, segmen ST 0,17 detik, gelombang T 0,17 mV dan MEA 83,6°. Pada hasil K2 frekuensi denyut jantung 122 x/menit, ritme jantung reguler, durasi P 0,06 mm/detik, amplitudo P 0,23 mV, interval PR 0,14 detik, amplitudo R 0,80 mV, interval QRS 0,04 detik, interval QT 0,16 detik, segmen ST 0,14 detik, gelombang T 0,12 mV dan MEA 68,6°. Kombinasi ketamin-medetomidin menghasilkan kualitas anestesi yang baik untuk kardiovaskular.

Kata kunci: acepromazin, elektrokardiogram, ketamin, medetomidin, babi

INTRODUCTION

Pigs are often used in the translational research, animal models for surgical techniques, and procedural training (Morgaz, 2015). The advantage of using pigs in various studies is because this species have several similarities with humans, including the cardiovascular, integumentary, digestive, and urinary systems (Tsang *et al.*, 2016). In addition, pigs are a common animal model of cardiovascular injury and intervention, but because pigs are difficult to control effectively, anesthesia procedure is needed (Lehmann *et al.*, 2017).

Ketamine is an anesthetic which has analgesic and cataleptic properties with short work. Ketamine stimulates the cardiovascular system which results in an increase in heart rate, blood pressure, and cardiac output through the action of the sympathetic nervous system (Hernández *et al.*, 2019). Another anesthetic is medetomidine which is an α_2 -adrenoreceptor agonist that has analgesic, muscle relaxing, and anxiolytic

properties (Kanda *et al.*, 2019). However, medetomidine has several pharmacological effects such as suppressing the central nervous system, peripheral and cardiac vasoconstriction, bradycardia, respiratory suppression, and hypothermia (Canpolat *et al.*, 2016). Acepromazine can be used as antiemetic, anticonvulsant, antispasmodic, hypotensive, hypothermic, and muscle relaxing properties but has no analgesic effects. Additionally, acepromazine produces the longest recovery and has a short half-life (Yohannes *et al.*, 2018). Administration of acepromazine with a higher dose may not increase sedation, but it can prolong the side effects. Anesthetic drugs such as ketamine, medetomidine, and acepromazine can be used singly (one type) or a combination to obtain and/or prolong the desired effect (Mikolajczyk, 2016).

In anesthetic procedure, ketamine is rarely used singly because it causes poor relaxation, catalepsy, muscle stiffness, and increase heart rate. For these reasons, ketamine is generally combined with

medetomidine and acepromazine. The combination of ketamine and medetomidine can cause seizures and poor recovery even in low doses while administration in high doses causes bradycardia and increase respiratory rate (Hollis *et al.*, 2020). The effects of cardiovascular depression caused by medetomidine are overcome by administering ketamine to increase the frequency of the heart rate and prevent it from significant decrease (Canpolat *et al.*, 2016). The combination of ketamine-acepromazine can increase heart rate, seizures, and vomiting where both of which are the effects of ketamine (Adel *et al.*, 2017). According to Yohannes *et al.* (2018), administration of 0.01 mg/kg and 5 mg/kg acepromazine-ketamine resulted in significant increased in heart rate.

Anesthesia administration can have an effect on cardiovascular function, such as increased or decreased heart work, tachycardia, bradycardia, hypertension, and hypotension. These conditions have an impact on changes in the anatomy and/or cardiac function that cause morbidity and or mortality (Staikou *et al.*, 2014). Changes in heart function can be detected by electrocardiogram (ECG). Electrocardiography is a tool to measuring the biopotential electricity of the heart which is described in the form of P, Q, R, S, and T waves (Taati and Raisi, 2017). Therefore, this study aims to determine the effect of anesthetic combination of ketamine-medetomidine and ketamine-acepromazine on the value and ECG images of pigs.

MATERIALS AND METHODS

This research was conducted at the Animal Education Hospital (RSHP), Faculty of Veterinary Medicine, Bogor Agricultural University (IPB). Acclimatization and maintenance of animals carried out in the Animal Facility at the Laboratory Animal Management Unit (UPHL), Faculty of Veterinary Medicine (IPB). All procedures in this study were approved by the Animal Ethics Commission of IPB (Number: 152/KEH/SKE/X/2019).

This study used six pigs (*Sus scrofa*) aged 2-3 months with a body weight of 25-30 kg. Before treatment, animals were conditioned without feeding for 12 hours and water for 4 hours. Afterwards, all pigs were induced with combination of ketamine (10 mg/kg BW) - medetomidine (0.08 mg/kg BW) and ketamine (22 mg/kg BW)-acepromazine (1.1 mg/kg BW) (Flecknell,

2015). The anesthetic combinations were injected simultaneously with different syringes intramuscularly. After the animals were anesthetized at the surgical stage, it was tested on pain relief by pinching the ears, tail, and interdigitates, then loss of reflexes in the palpebra, pupils, and pedals, and also the direction of the eyeball towards the ventrokanthus, ECG recording was performed. Furthermore, ECG recording was performed using the Fukuda M-E ZL-501 electrocardiographic device. The recording electrodes were placed on the right and left wrists and then on the right and left ankles. The voltage used for ECG recording was 1 voltage (1 cm = 1mV) with a recording speed of 25 mm/sec. The variables observed were heart rate frequency, P duration, P amplitude, PR interval, R amplitude, QRS interval, QT interval, ST segment, T wave, Mean Electrical Axis (MEA) and heart rhythm. The results of the study were analyzed using a two-group t-test at 5% significance level.

RESULTS AND DISCUSSION

The average heart rate frequency, P duration, P amplitude, R amplitude, PR interval, QRS, QT, ST segment, T wave, and MEA resulted by a combination of ketamine-medetomidine and ketamine-acepromazine anesthesia are presented in Table 1. The average of heart rate frequency in the K1 and K2 treatments were 100 ± 23.12 x/min and 122 ± 19.63 x/min, respectively. Normal heart rate frequency values according to Zhang *et al.* (2016) range from 82-172 x/minute. The use of anesthetic combination did not show any significant difference ($P > 0.05$) in heart rate frequency. In K1, the heart rate was lower than that of K2 because the ketamine-medetomidine combination had a cardiovascular effect characterized by bradycardia, decreased cardiac output, and arterial hypertension (Canpolat *et al.*, 2016). The combination of ketamine-medetomidine can provide immobilization and excellent relaxation in a variety of animal species. Acepromazine is a tranquilizer that does not suppress the cardiovascular system. As a result, the frequency of the heart rate increases higher in the ketamine-acepromazine group than in the ketamine-medetomidine group (Alishahi *et al.*, 2019). A higher dose of ketamine also caused higher increase in heart rate frequency in K2 than in K1.

Table 1. Results of ECG leads II in pigs (*Sus scrofa*) at the surgical stage with a combination of ketamine-medetomidine (K1) and ketamine-acepromazine (K2)

Parameter	Treatment		(P-value)
	K1	K2	
Heart Rate (x/minute)	100 ± 23.12	122 ± 19.63	0.271
Duration P (seconds)	0.07 ± 0.01	0.06 ± 0.02	0.705
P Amplitude (mV)	0.27 ± 0.02	0.23 ± 0.04	0.253
PR Interval (seconds)	0.17 ± 0.03	0.14 ± 0.01	0.139
R Amplitude (mV)	0.75 ± 0.17	0.80 ± 0.25	0.788
QRS Interval (seconds)	0.05 ± 0.01	0.04 ± 0.01	0.269
QT Interval (seconds)	$0.20 \pm .02$	0.16 ± 0.06	0.361
ST Segment	$0.17 \pm .01$	0.14 ± 0.07	0.603
T Wave (mV)	0.17 ± 0.05	$0.12 \pm .22$	0.742
Mean Electrical Axis (degree)	83.6 ± 22.1	68.6 ± 9.81	0.343

K1= Combination of ketamine-medetomidine, K2= Combination of ketamine-acepromazine

The average duration of P in the K1 and K2 treatments were 0.07 ± 0.01 and 0.06 ± 0.02 seconds, respectively. The results of statistical tests show that the two anesthetic combination treatments showed no significant difference ($P>0.05$). According to Zhang *et al.* (2016) the normal value of P duration in pigs ranges from 0.02-0.06 seconds. Atrial depolarization in the ketamine-medetomidine combination causes a slowdown so the duration of P increases. This indicates an enlargement of the electric potential of the heart of pigs that were given ketamine-medetomidine anesthesia. The shape and duration of the P wave can indicate enlargement of the atrium (Lusiana, 2016).

The average P amplitudes in the K1 and K2 treatments were 0.27 ± 0.02 , and 0.23 ± 0.04 mV, respectively. These values were greater than the average reported by Zhang *et al.* (2016) which is 0.04-0.18 mV. However, the two anesthetic combination treatments did not show any significant difference ($P>0.05$). The amplitude P describes the amount of the electrical activation of the in the myocardial atria of the heart during atrial depolarization. According to Franco *et al.* (2018), administration of 40 mg ketamine causes a significant increase in mitral flow because ketamine induces a positive inotropic effect at relevant concentrations. The occurrence of an increase in P amplitude is associated with an increase in heart rate frequency, increase in cardiac conduction of the electrical impulses and heart muscle contractions (Lusiana, 2016). Ketamine-medetomidine stimulates vagal tone, causing vascular vasoconstriction (Gargiulo *et al.*, 2012).

The PR intervals for the K1 and K2 treatments were 0.17 ± 0.03 and 0.14 ± 0.01 seconds, respectively. This result is higher than the mean PR interval reported by Zhang *et al.* (2016), which is 0.03-0.12 seconds. The two anesthetic combination treatments also showed no significant difference ($P>0.05$). Ketamine can alter the electrical activity of the heart and prolong the PR interval but does not affect ECG waveforms (Adams, 2001). Ketamine-medetomidine causes prolongation of the PR interval due to increased parasympathetic activity (first degree AV Block) (Gargiulo *et al.*, 2012). The combination of ketamine-acepromazine inhibits central intraneural transmission thereby increasing muscle relaxation and analgesia (Yohannes *et al.*, 2018).

The R amplitudes in the K1 and K2 treatments were 0.75 ± 0.17 mV and 0.80 ± 0.25 mV, respectively, where these combinations show no significant differences ($P>0.05$). These findings are still in the normal range as reported by Zhang *et al.* (2016), which is 0.11-1.51, because combination of ketamine-medetomidine causes inhibition of electrical conduction in the ventricles of the heart and Purkinje fibers, resulting in a decrease in the strength of electrical impulses in the ventricles compared to the combination of ketamine-acepromazine (Carareto *et al.*, 2008). Very high R waves can cause ventricular hypertrophy because hypertrophic muscles require a very strong electric current for depolarization (Lusiana, 2016).

The QRS intervals in the K1 and K2 were 0.05 ± 0.01 and 0.04 ± 0.01 seconds, respectively where the results did not differ statistically ($P>0.05$). In the

normal pigs, the QRS interval value is 0.03 to 0.08 seconds (Zhang *et al.*, 2016). Animals induced by ketamine-medetomidine showed a good QRS interval results when the animals were anesthetized. This is because the electrical impulses from the sinus atrial nodes that are passed to the atrioventricular nodes through His bundles to the Purkinje fibers making contact with the ventricular cells for impulse flow (Lusiana, 2016). Furthermore, the QRS interval value is lower because due to the administration of the ketamine-acepromazine combination because acepromazine is a tranquilizer that does not suppress the cardiovascular system, therefore the contraction of the heart muscle increases and causes the dimensions of the ventricular space to narrow (Pachon *et al.*, 2015).

The QT intervals in the K1 and K2 were 0.20 ± 0.02 and 0.16 ± 0.06 seconds, respectively. The results of the study by Zhang *et al.* (2016) showed that the QT interval in normal pigs is 0.13 to 0.32 seconds. The results of two anesthetic combination treatments showed no significant difference ($P>0.05$). The combination of anesthetics did not cause changes in ventricular repolarization. This is in accordance with the research of Franco *et al.* (2018), which stated the QT interval in the administration of ketamine with a constant rate of infusion measured from the start and during observation was slightly higher. According to Sudisma (2012), giving alpha 2 adrenoreceptors can prolong the QT interval. If the heart rate is getting slower than the QT interval is getting longer. Increasing the duration of the QT interval can cause arrhythmias (Diniz *et al.*, 2017)

The ST segments in the K1 and K2 were 0.17 ± 0.01 and 0.12 ± 0.22 , respectively. Rubio *et al.* (1989) stated that ST segment in normal pigs is 0.071 to 0.209 seconds. The ST segments values between two groups did not show a significant difference ($P>0.05$). The ST segment will experience an increase in duration and delay in initiation of ventricular myocardial repolarization with physical maturation and age (Fernández *et al.*, 2003). Additionally, the ST segment can be used to detect the presence of myocardial infarction on the ECG record (Surtono *et al.*, 2016).

The T waves found in this study were 0.17 ± 0.05 and 0.12 ± 0.22 mV, respectively. The results of T waves in K1 and K2 show that both anesthetic combinations showed no significant difference ($P>0.05$). According to research by Arjentina (2012), the amplitude of the T wave is relatively stable after the administration of gravimetric IV drip anesthesia with ketamine, propofol or a combination thereof. This means that the strength of the electrical impulses at the time of ventricular repolarization is not affected by the administration of ketamine-medetomidine and ketamine-acepromazine anesthetics. Normally the T waves in piglets can be negative and positive (Richig and Sleeper, 2014). According to Raisi *et al.* (2019), the ECG results in ducks and raptors who experienced an increase in the T wave indicated hyperkalemia. T waves can indicate ischemic/infarction and electrolyte abnormalities.

MEA values in K1 and K2 were 83.6 ± 22.1 and 68.6 ± 9.81 degrees, respectively. Zhang *et al.* (2016)

reported that the axis value of the pig is -1600 ± 1700 , meaning that the values in this study are still within the normal range. The results of statistical tests show that the two anesthetic combination treatments showed no significant difference ($P > 0.05$). The axis value is the electricality of the heart obtained from the EKG, namely the Q, R, S amplitudes in Leads I, II, and III (Suprayogi, 2009).

In this study, all pigs had a normal heart rhythm after anesthetized with ketamine-medetomidine combination. This is illustrated in the ECG recording shown by a P wave, followed by the QRS complex (Lusiana, 2016). The normal heart rate in a pig is 82-172. Values below 82 x/minute are called bradycardia, while values above 172 x/minute are called tachycardia (Rubenstein et al., 2007).

CONCLUSION

Based on the results of this research, it can be concluded that the administration of the anesthetic combination of ketamine-medetomidine and ketamine-acepromazine does not have a different effect. The administration of the ketamine-acepromazine combination increases the heart rate compared to the ketamine-medetomidine combination, so that, this combination is less suitable for cardiovascular surgery treatment.

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