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Domestic Pigs as an Animal Model of Myocardial Infarction: a Comparison of Systolic and Diastolic Blood Flow Velocities of Cardiac Valves

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ABSTRACT

Cardiovascular disease (CVD) is still the leading cause of death according to WHO in 2021. CVD generally results in myocardial infarction (MI), which occurred after tissue ischemia. Echocardiography is most likely a diagnostic tool without invasive effects. This study aimed to compare the blood flow in pig research animals treated with ligases of the circumflex arteries. Measurements were made in the mitral valve (MV), tricuspid valve (TV), semilunar pulmonary valve (SLP), and semilunar aortic valve (AO) of velocity during systole (Vs), velocity during diastole (Vd), time average peak velocity (TAMAX), and blood flow pressure at three-time points: before ligase treatment, after acute infarction (60 min), and 8 weeks after ligase treatment. All parameters in MV group increased at 60 min and decreased at 8th weeks. On TV, TAMAX and pTAMAX decreased at 60 min and week 8. In SLP, VS, pVS, and Vd decreased at 60 min and increased at 8th week. The pVd and pTAMAX parameters decreased at 60 min and 8th week, while TAMAX increased at 60 min and decreased at 8th week. In AO, the TAMAX and pTAMAX parameters increased at 60 min and 8 weeks; the other parameters were similar to MV and TV patterns.
Keywords: echocardiography, myocardial infarction, pig model, pressure, velocity

ABSTRAK

Penyakit kardiovaskular (PKV) merupakan penyebab utama kematian global menurut WHO pada tahun 2023. Infark miokard (MI), sebagai komplikasi utama PKV, terjadi akibat iskemia jaringan. Ekokardiografi merupakan modalitas diagnostik non-invasif yang digunakan untuk menilai fungsi kardiovaskular. Penelitian ini bertujuan untuk membandingkan aliran darah pada model hewan babi dengan MI yang diinduksi melalui ligasi arteri sirkumfleks. Pengukuran dilakukan pada katup mitral (MV), katup trikuspid (TV), katup pulmonal semilunar (SLP), dan katup aorta semilunar (AO). Parameter yang dinilai meliputi kecepatan sistol (Vs), kecepatan diastol (Vd), waktu kecepatan puncak rata-rata (TAMAX), serta tekanan aliran darah (pVs, pVd, pTAMAX) pada tiga titik waktu: sebelum ligasi, 60 menit setelah infark akut, dan delapan minggu pasca-ligasi. Hasil menunjukkan bahwa seluruh parameter MV meningkat pada menit ke-60 dan menurun pada minggu ke-8. Pada TV, TAMAX dan pTAMAX menurun pada kedua titik waktu. Pada SLP, Vs, pVs, dan Vd menurun pada menit ke-60 dan meningkat kembali pada minggu ke-8. Pada AO, TAMAX dan pTAMAX meningkat secara progresif. Penelitian ini memberikan wawasan mengenai perubahan hemodinamik pasca-MI dan dapat menjadi dasar studi lebih lanjut dalam disfungsi kardiovaskular.
Kata kunci: ekokardiografi, infark miokard, model babi, tekanan, kecepatan

INTRODUCTION

Myocardial infarction (MI) is a pathological condition characterized by impaired or complete obstruction of blood flow to a specific region of the myocardium, leading to ischemia (Mihalko *et al.* 2018). Echocardiography is a widely used noninvasive diagnostic tool for detecting infarction and evaluating cardiac function (Nagueh *et al.* 2016) One key aspect of echocardiographic assessment is the evaluation of heart valve function, which can be determined by measuring blood flow velocity (Vs, Vd), blood flow pressure (pressure Vs, pressure Vd), and the time-averaged maximum velocity (TAMAX).

Blood flow velocity (Vs) represents the speed at which blood travels through the heart during systole, when the myocardium contracts and pumps blood into the arteries. Conversely, diastolic velocity (Vd) measures blood flow during diastole, when the heart relaxes and fills with blood (Hori *et al.* 2008). An abnormally high Vs may indicate valvular stenosis or increased vascular resistance, whereas a low Vs may suggest diastolic dysfunction or valvular regurgitation. Evaluating velocity parameters provides insight into myocardial contraction and relaxation efficiency and can help detect obstructions or regurgitation within the heart valves.

Pressure Vs refers to the pressure gradient across the heart valves during systole, which is crucial for diagnosing valvular stenosis. A higher-pressure gradient suggests increased obstruction, whereas lower values may indicate reduced cardiac efficiency. Assessing pressure velocity is vital in determining the severity of valvular disease and its impact on overall cardiac function. Similarly, TAMAX provides critical information about valvular abnormalities and their effects on hemodynamics. It is particularly useful in assessing heart valve stenosis, as higher values indicate increased pressure gradients and potential narrowing of the valve orifices.

In MI, ischemic damage occurs due to obstruction of coronary arteries, which supply oxygen and nutrients to the myocardium (Pustjens *et al.* 2020). The coronary circulation consists of the left and right coronary arteries, with the left coronary artery further branching into the left anterior descending and circumflex arteries, while the right coronary artery gives rise to the right posterior descending and marginal arteries (Tamis-Holland *et al.* 2019; Zhang 2022). Due to their narrow lumens, coronary arteries are highly susceptible to blockages (Smit *et al.* 2020).

The development of myocardial infarction models in pigs is of significant importance for cardiovascular research. While this model has not been fully established in biomedicine, it provides a valuable platform for translational studies. MI in pigs is typically induced via surgical thoracotomy, during which small coronary arteries are ligated to replicate infarction conditions observed in humans (Solanes *et al.* 2022). This procedure exposes the heart, allowing for precise ligation of target arteries. The resulting ischemia and occlusion levels can be controlled to assess the extent of myocardial damage.

Establishing MI using ligation models is crucial for preclinical studies aimed at developing therapeutic interventions (Kainuma et al. 2017; De Villiers dan Riley 2020). Monitoring myocardial function before, immediately after, and at later stages of infarction is essential for evaluating the efficacy of treatments such as stem cell therapy, which has emerged as a potential alternative for myocardial repair.

Echocardiography plays a pivotal role in assessing cardiac function by measuring blood flow velocity and pressure across heart valves. Among various ultrasound techniques, Pulsed Wave Doppler (PW Doppler) provides real-time, noninvasive measurements of blood flow velocity with high spatial accuracy. This technique allows for precise velocity assessment at specific anatomical locations, making it an invaluable tool for cardiovascular diagnostics.

This study aims to evaluate blood flow velocity during systole (Vs) and diastole (Vd), time-averaged maximum velocity (TAMAX), systolic flow pressure (pressure Vs), diastolic flow pressure (pressure Vd), and TAMAX pressure at three distinct time points: before infarction, immediately after infarction, and eight weeks post-infarction.

MATERIALS AND METHODS

This experiment involved the use of domestic pigs to create a model of myocardial infarction. Infarction was created by ligating the circumflex artery, the first branch of the left coronary artery. The ligation results were validated by diagnostic electrocardiography (ECG) which showed ST segment elevation and measured the infarct area in the heart, 60 minutes after ligation and 8 weeks after treatment. The animals were kept for 8 weeks.

The research sample consisted of pigs (*a domestic pig*) with body weights ranging between 35 and 45 kg and aged between 3 and 4 months. Pigs were kept in individual pens with a pen area of 3 × 4 m, with *humidity* of 70%. Exposure to light and dark followed the solar cycle at a temperature of 25 – 30 °C. Animals were provided an unlimited supply of water (*ad libitum*) and special feed for pigs. The research was carried out after obtaining ethical approval to use experimental animals (certificate number 152/KEH/SKE/X/2021)

and obtaining permission from the research animal maintenance facility (RSHP SKHB IPB).

The pigs used have been confirmed to be in clinical health and have been acclimatized for 10–14 days (Albus 2012). Animal acclimatization was carried out to adapt to the research cage facilities and standardize the animal's physiological status, namely by administering anthelmintic drugs (albendazole) at a dose of 5–10 mg/kg BW *orally* (PO), antiprotozoal (trimethoprim) dose of 48 mg/kg BW every 24 h (IM), anti-ectoparasitic (*ivermectin*) dose 300 µg/kg BB *subcutaneously* (SC), and antibiotic (Penicillin G) dose of 6600 units/kg/day for 4 days (IM).

Surgery was initiated the day before the tracheostomy. A clinical examination was carried out to obtain body weight data, and the animal was bathed and fasted (food fast) for at least 12 hours and 4 hours before anaesthesia. Echocardiography data were collected three times, namely, 0 min, 60 min, and 8 weeks after blood vessel ligation. The TDI velocity locations were measured at the lateral corner of the mitral, tricuspid semilunar pulmonary, and semilunar aorta valve annulus according to (Hori *et al.* 2008). The echocardiography data parameters included data velocity during systole and diastole, *pressure* (Vs and Vd), TAMAX, and *Pressure* (TAMAX). Using a low-wall-filter setting (100–200 MHz) and low signal gain (Nagueh *et al.* 2016).

The data obtained are presented as the mean ± standard deviation in the qualitative descriptive narrative, while the quantitative data were tested statistically using one-way or two-way analysis *of variance* (ANOVA) and continued with the Duncan Multiple Distance Test (UJBD) if a difference occurred. Statistical significance was defined as $P < 0.05$. Data were analyzed using SPSS for Windows® and Microsoft Excel® software (SPSS Inc.,)

RESULTS

Hemodynamic Assessment in Myocardial Infarction Pigs

Data Collection and Analysis

Velocity (Vs, Vd), pressure (Pressure Vs, Vd), and time-averaged maximum velocity (TAMAX) data were collected from nine pigs at three-time points of examination: before infarction, immediately after infarction, and eight weeks post-infarction. Measurements were obtained using echocardiography-supported diagnostic tools and focused on the mitral, tricuspid, aortic semilunar, and pulmonary semilunar valves. Flow velocity and pressure were analyzed for each valve (Tables 1–4), with results visualized in graphs for comparative analysis.

Mitral Valve

Table 1 shows no significant differences in all mitral valve parameters ($p > 0.05$). Velocity (Vs, Vd), TAMAX, and pressure measurements increased at 60 minutes but declined at eight weeks. Figure 1 confirms that Vs and Vd peaked at 60 minutes and subsequently decreased. While blood pressure (Pressure Vd) also rose at 60 minutes, it returned to baseline at eight weeks. Figure 2 further illustrates that TAMAX and TAMAX pressure were highest at 0 minutes, followed by a decline at 60 minutes and eight weeks.

Table 1. Mitral valve values in pigs with myocardial infarction

Parameters	Observation times			p-value
	0 minute	60 minute	8 weeks	
Vs (cm/s)	111.79 ± 36.67[a]	200.36 ± 98.06[a]	132.20 ± 9.84[a]	0.252
Pressure Vs (mmHg)	5.58 ± 3.07[a]	17.95 ± 16.77[a]	7.25 ± 0.93[a]	0.319
Vd (cm/s)	78.38 ± 28.85[a]	93.57 ± 32.20[a]	87.00 ± 13.07[a]	0.782
Pressure Vd (mmHg)	3.11 ± 1.98[a]	3.86 ± 2.40[a]	3.33 ± 0.62[a]	0.877
TAMAX (cm/s)	26.61 ± 14.83[a]	42.90 ± 3.85[a]	28.09 ± 19.24[a]	0.362
Pressure TAMAX (mmHg)	0.36 ± 0.29[a]	0.81 ± 0.17[a]	0.42 ± 0.42[a]	0.225

Note : Data are presented in mean form with standard deviation (x ± SD). The superscript letter (a) which is not different indicates there is no significant difference (P>0.05)

Tricuspid Valve

As shown in Table 2, no significant differences were observed in Vs, pressure velocity, or TAMAX ($p > 0.05$). In control+ pigs, Vs and Pressure Vs were highest at 60 minutes, followed by 0 minutes, and lowest at eight weeks. Conversely, Vd and Pressure Vd peaked at 60 minutes, decreased at eight weeks, and were lowest at 0 minutes. TAMAX and Pressure TAMAX followed a different pattern, with the highest values at 0 minutes, declining at 60 minutes, and reaching their lowest point at eight weeks. Figures 3 and 4 confirm that tricuspid valve values peaked at 60 minutes before decreasing at eight weeks.

Pulmonary Semilunar Valve

Table 3 indicates no significant differences in pulmonary valve parameters ($p > 0.05$). Vs and Vd were highest at 0 minutes, followed by eight weeks, with the lowest values at 60 minutes. Pressure Vd and Pressure TAMAX showed peak values at 0 and 60 minutes, declining at eight weeks. TAMAX values were highest at 60 minutes and eight weeks, with the lowest recorded at 0 minutes. Figure 5 further supports these findings, showing a decline from 0 to 60 minutes, followed by a slight increase at eight weeks. Similarly, Figure 6 reveals that Pressure Vs peaked at 0 minutes, declined at 60 minutes, and slightly increased at eight weeks.

Aortic Semilunar Valve

Table 4 shows no significant differences in aortic valve parameters ($p > 0.05$). Vs and Pressure Vs reached their highest values at 60 minutes, followed by eight weeks, with the lowest at 0 minutes. Vd and Pressure Vd peaked at 60 minutes, followed by 0 minutes, and were lowest at eight weeks. TAMAX and Pressure TAMAX exhibited the highest values at eight weeks, followed by 60 minutes, and the lowest at 0 minutes. Figure 7 confirms this trend, illustrating that Vs, Vd, and TAMAX values peaked at different time points. Similarly, Figure 8 highlights that Pressure Vs was highest at 60 minutes, followed by eight weeks,

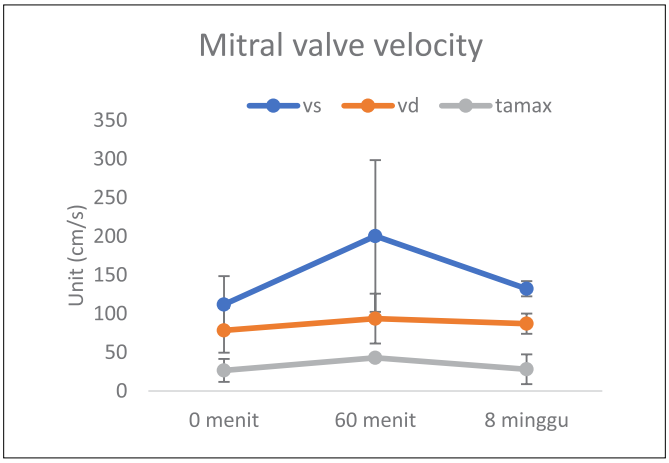

Figure 1. Mitral valve velocity systole (Vs), velocity diastole (Vd), and Time average maximum velocity (TAMAX)

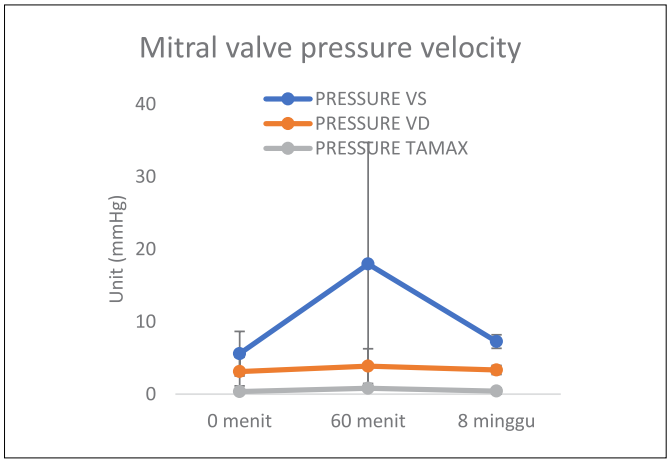

Figure 2. Mitral valve pressure velocity systole (Vs), pressure velocity diastole (Vd), and pressure Time average maximum velocity (TAMAX)

Table 2. Tricuspid Valve Values in pigs with myocardial infarction

Parameters	Observation times			p-value
	0 minutes	60 minutes	8 weeks	
Vs (cm/s)	123.53 ± 84.06[a]	142.77 ± 81.29[a]	92.65 ± 41.63[a]	0.703
Pressure Vs (mmHg)	8.29 ± 9.80[a]	10.06 ± 10.34[a]	3.77 ± 3.03[a]	0.659
Vd (cm/s)	51.98 ± 17.47[a]	81.39 ± 31.29[a]	64.74 ± 25.00[a]	0.414
Pressure Vd (mmHg)	1.22 ± 0.88[a]	3.26 ± 1.92[a]	2.14 ± 1.73[a]	0.348
TAMAX (cm/s)	42.06 ± 27.30[a]	41.08 ± 19.58[a]	22.40 ± 25.77[a]	0.571
Pressure TAMAX (mmHg)	0.97 ± 0.88[a]	0.83 ± 0.70[a]	0.38 ± 0.60[a]	0.621

Note : Data are presented in mean form with standard deviation (x ± SD). Superscript letters (a) that are not different in the same row indicate there is no significant difference (P>0.05)

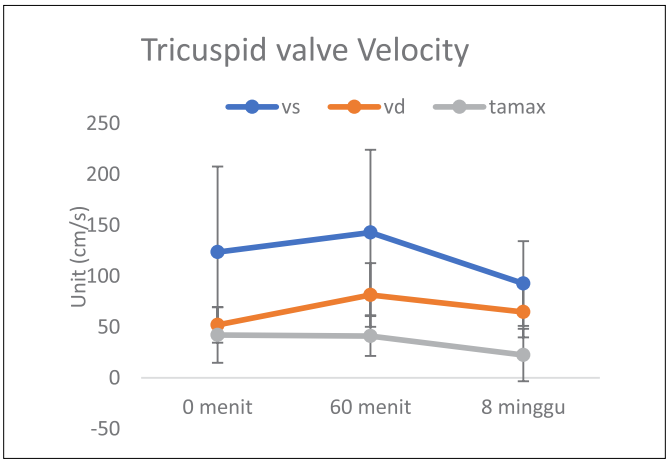

Figure 3. Tricuspid valve velocity systole (Vs), velocity diastole (Vd), and Time average maximum velocity (TAMAX)

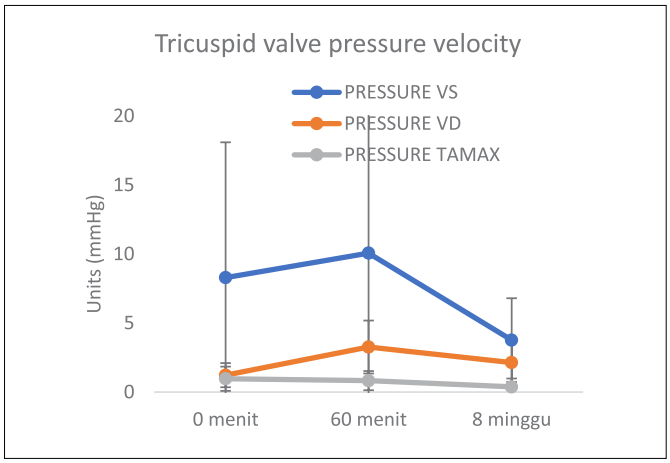

Figure 4. Tricuspid valve pressure velocity systole (Vs), pressure velocity diastole (Vd), and pressure Time average maximum velocity (TAMAX)

Table 3. Semilunar pulmonary valve values in pigs with myocardial infarction

Parameters	Observation Times			p-value
	0 minutes	60 minutes	8 weeks	
Vs (cm/s)	134.76 ± 51.14[a]	95.04 ± 20.34[a]	102.62 ± 48.08[a]	0.512
Pressure Vs (mmHg)	8.60 ± 5.42[a]	3.30 ± 2.13[a]	5.33 ± 4.07[a]	0.346
Vd (cm/s)	83.69 ± 64.58[a]	63.49 ± 43.56[a]	66.81 ± 20.19[a]	0.853
Pressure Vd (mmHg)	4.53 ± 4.79[a]	2.14 ± 2.32[a]	2.10 ± 1.40[a]	0.591
TAMAX (cm/s)	25.80 ± 32.13[a]	35.60 ± 8.33[a]	28.10 ± 22.44[a]	0.866
Pressure TAMAX (mmHg)	1.89 ± 3.19[a]	0.56 ± 0.20[a]	0.48 ± 0.59[a]	0.612

Note: Data are presented in mean form with standard deviation (x ± SD). Superscript letters (a) that are not different in the same row indicate there is no significant difference (P>0.05)

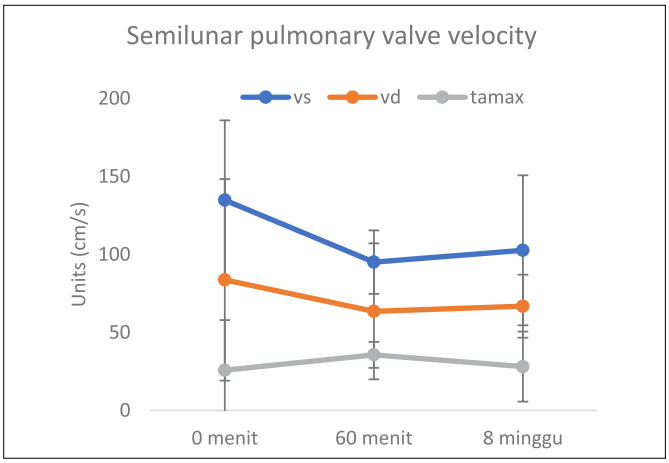

Figure 5. Semilunar Pulmonary valve velocity systole (Vs), velocity diastole (Vd), and Time average maximum velocity (TAMAX)

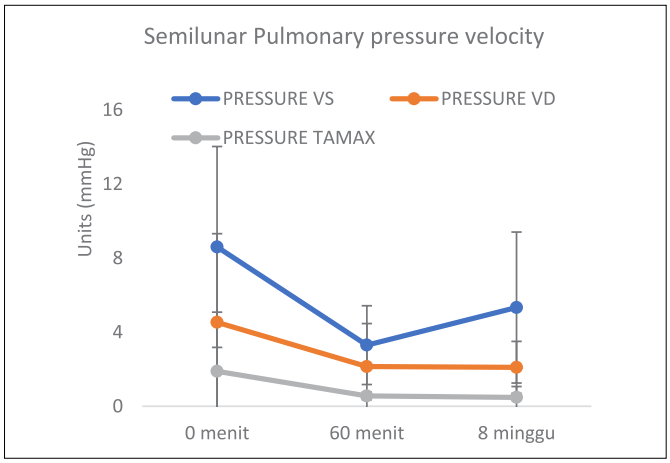

Figure 6. Semilunar Pulmonary valve pressure velocity systole (Vs), pressure velocity diastole (Vd), and pressure Time average maximum velocity (TAMAX)

Tabel 4. Semilunar Aorta valve values in pigs with myocardial infarction

Parameters	Observation Times			p-value
	0 minutes	60 minutes	8 weeks	
Vs (cm/s)	113.73 ± 67.40[a]	153.29 ± 23.14[a]	131.20 ± 50.02[a]	0.648
Pressure Vs (mmHg)	6.64 ± 7.22[a]	8.06 ± 2.51[a]	7.57 ± 4.66[a]	0.944
Vd (cm/s)	74.87 ± 28.66[a]	89.85 ± 17.89[a]	71.74 ± 44.90[a]	0.774
Pressure Vd (mmHg)	2.94 ± 2.69[a]	3.30 ± 1.24[a]	2.67 ± 2.58[a]	0.943
TAMAX (cm/s)	8.82 ± 2.18[a]	21.02 ± 11.67[a]	35.08 ± 14.93[a]	0.070
Pressure TAMAX (mmHg)	0.03 ± 0.02[a]	0.24 ± 0.21[a]	0.58 ± 0.46[a]	0.140

Note : Data are presented in mean form with standard deviation (x ± SD). Superscript letters (a) that are not different in the same row indicate there is no significant difference (P>0.05)

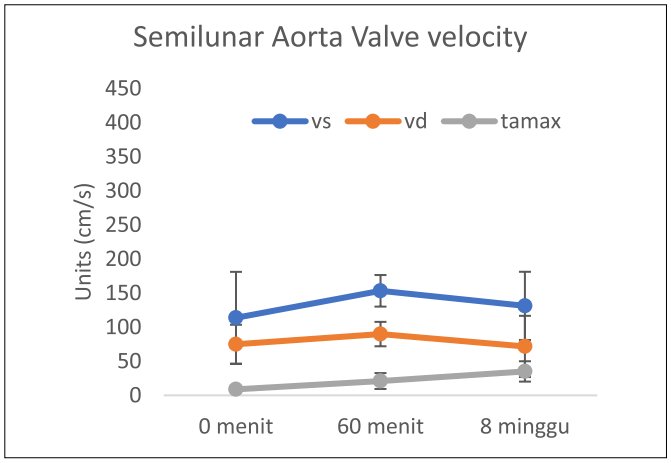

Figure 7. Semilunar Aorta valve velocity systole (Vs), velocity diastole (Vd), and Time average maximum velocity (TAMAX)

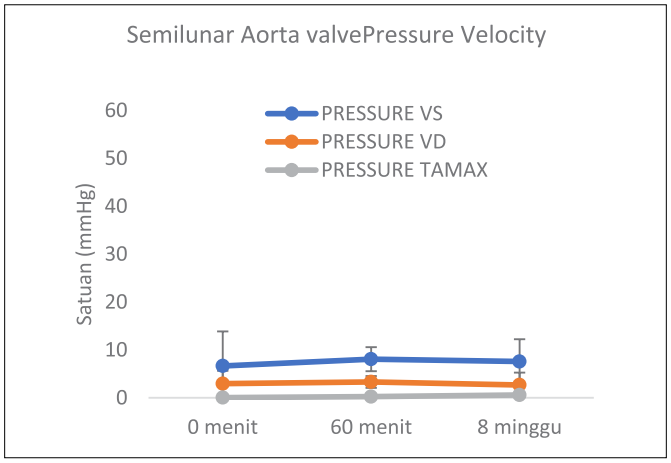

Figure 8. Semilinar Aorta valve pressure velocity systole (Vs), pressure velocity diastole (Vd), and pressure Time average maximum velocity (TAMAX)

and lowest at 0 minutes. No significant changes were observed in AO values within the control+ treatment group.

DISCUSSION

This study aimed to evaluate differences in blood flow velocity (Vs, Vd) and pressure (Pressure Vs, Pressure Vd, TAMAX) in myocardial infarcted pigs at three-time points: before infarction (0 min), immediately post-infarction (60 min), and eight weeks post-infarction. Measurements were obtained using echocardiography, focusing on the four cardiac valves—mitral, tricuspid, aortic semilunar, and pulmonary semilunar. Observations were performed under anaesthesia.

Echocardiographic findings showed no statistically significant differences in hemodynamic parameters across the three-time points. At 60 minutes, blood flow velocity and pressure tended to increase compared to 0 minutes, reflecting an acute stress response following ligation. However, these values returned to baseline at eight weeks, likely due to myocardial remodelling and revascularization. The absence of significant changes in velocity and pressure at 0 and 60 minutes suggests either an insufficient ischemic effect at the infarct site or an early echocardiographic assessment, as infarction is typically confirmed 24 hours post-ligation (Mahdiui *et al*. 2021).

Within one hour after ligation, increased blood flow and blood pressure occur in response to the initial ischemic stress, triggered by activation of the sympathoadrenergic system, redistribution of blood flow, metabolic changes, and increased cardiac wall stress. Sympathetic nervous system activation increases catecholamine release, causing peripheral vasoconstriction, increased myocardial contractility, and tachycardia to maintain perfusion to vital tissues. Vascular autoregulation mechanisms can cause a coronary steal phenomenon, in which more blood flows to the non-ischemic area, worsening hypoperfusion in the affected area. Metabolically, the shift from

aerobic to anaerobic metabolism causes lactate accumulation, metabolic acidosis, and disturbances in ion homeostasis, including increased intracellular Na^+ and Ca^{2+} leading to cellular edema and contractile dysfunction. Cardiac wall stress also increases due to increased preload and afterload as a compensatory response to hypoperfusion. Myocardial damage at this stage is still reversible, especially in the first hour, because the contractile dysfunction that occurs is still in the ischemic stunning phase, where myocardial cells remain alive but experience temporary dysfunction. If perfusion is restored in less than two hours, most ischemic tissue can recover without permanent damage, but if ischemia continues for more than 20–30 minutes, cell membrane injury begins to occur, and after three to six hours, myocardial necrosis becomes more extensive and irreversible. Therefore, rapid reperfusion in the early phase is very important to prevent the development of permanent infarction and reduce the long-term impact of ischemic injury(Uygur dan Lee 2016; Broughton *et al.* 2018; Damluji *et al.* 2021).

Post-infarction remodelling processes, including inflammation, scar formation, and angiogenesis, contributed to functional recovery at eight weeks (Spadaccio *et al.* 2022; Hilgendorf *et al.* 2024). Angiogenesis and arteriogenesis facilitated improved myocardial perfusion, while endothelial dysfunction and fibrosis influenced long-term outcomes. The infarct size and ligation location significantly impacted hemodynamic responses, as smaller infarct areas may not induce detectable changes in blood flow velocity(Cui *et al.* 2022).

Echocardiographic examination in anaesthetized pigs also revealed hemodynamic variations due to anaesthetic effects. Propofol, commonly used in cardiovascular studies, induces hypotension by decreasing vascular resistance and myocardial contractility(Cobo *et al.* 2020). This may have contributed to the absence of significant differences between time points, as anaesthesia can modulate cardiac output, heart rate, and blood pressure responses (Reindl *et al.* 2020).

In conclusion, velocity and pressure parameters measured at 0 min, 60 min, and 8 weeks post-ligation showed no statistically significant changes. However, graphical data indicated an increase in flow at 60 minutes with a subsequent normalization at eight weeks. Flow pressure decreased at 60 minutes but increased at eight weeks, suggesting an inverse relationship between flow and pressure in the acute phase of infarction. These findings highlight the dynamic nature of myocardial ischemia and recovery, influenced by both physiological adaptation and external factors such as infarct size and anaesthetic effects.

The results of hemodynamic observations in a myocardial infarction model in pigs indicate that the increase in blood flow and pressure one hour after ligation is due to a sympathoadrenergic compensatory response, while recovery after eight weeks is related to the mechanism of angiogenesis and revascularization. Changes in blood flow and pressure parameters in the four heart valves can be used to assess the severity of infarction and the effectiveness of reperfusion or regenerative therapy. The effect of anesthesia on cardiovascular parameters also needs to be taken into account in the study design for more valid results. This study provides important insights into optimizing a myocardial infarction model in pigs to support the development of myocardial infarction therapy in humans.

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"The author declares that there is no conflict of interest with the parties involved in this research."

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