Original Article

The effects of propofol on Doppler echocardiographic values of the aorta, main pulmonary artery, and mitral E wave in New Zealand white rabbits

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Abstract

The aim of this study was to determine the effects of propofol on acceleration time (AT), ejection time (ET), AT / ET ratio obtained from the aorta (Ao) and main pulmonary artery (MPA) and Doppler echocardiographic values of mitral E wave (E) in New Zealand white rabbits. Echocardiographic evaluation was performed in 40 conscious rabbits and repeated after propofol administration. The baseline mean values were 0.028±0.006 second (s) for Ao-AT, 0.116±0.017 s for Ao-ET, 0.24±0.036 for Ao-AT / ET, 0.05±0.01 s for MPA-AT, 0.137±0.018 s for MPA-ET, 0.38±0.037 s for MPA-AT/ET, 84.13±18.26 cm/s for E peak velocity, 3.06±1.38 mmHg for E peak pressure, 0.069±0.018 s for E duration, 0.046±0.015 s for E deceleration time (Edec). After propofol administration, the decrease in velocity (P = 0.044, 90.76±14.39 vs. 83.04±12.24) and peak pressure gradient (P = 0.036, 3.47±1.01 *vs.* 2.98±0.77) of Ao wave, as well as left ventricular ejection fraction (EF) and fractional shortening (FS) was statistically significant (P < 0.001, 70.1±4.47 *vs.* 63.2±3.79, 37.85±3.74 *vs.* 32.15±2.43, respectively); AT was longer (P < 0.05) and AT/ET was increased (P < 0.001) in both Ao and MPA. Among Doppler echocardiographic parameters of the E wave, there was only a statistically significant difference for Edec (P = 0.008). In the presented study, while the effect of propofol is minimal on Edec, its effects on aortic and pulmonic AT/ET values, as well as EF and FS values, should be taken into consideration.

Keywords: acceleration and ejection time, aorta, echocardiography, main pulmonary artery, propofol, rabbit

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Introduction

It is observed that cardiovascular diseases are at a significant rate in rabbits, which have become popular pets (Orcutt and Malakoff, 2021). Review articles on cardiac and cardiovascular diseases have been published (Pariaut, 2009; Reusch, 2005; Schnellbacher *et al*., 2012), and these diseases are discussed in textbooks (Orcutt and Malakoff, 2021; Varga, 2014). The effective use of advanced diagnostic methods such as echocardiography has recently enabled these diseases to be diagnosed more frequently. The prevalence of cardiovascular disease is 2.6%, and the rate of degenerative valve diseases is 40.5% in pet rabbits (Ozawa *et al*., 2021). In addition, rabbits are generally preferred for experimental degenerative valve disease (Hara *et al*., 2018; Kim *et al*., 2023; Lee *et al*., 2023; Szekeres *et al*., 2023).

Echocardiographic parameters of mitral flow are commonly used to evaluate the left ventricular (LV) function. One of the echocardiographic parameters used to evaluate diastolic function in human medicine is the measurement of early diastolic mitral inflow wave (E) deceleration time (DT). Shortened or longer Edec is a marker of increased LV chamber stiffness or impaired left ventricular relaxation, respectively (Dori *et al*., 2014). The ratio of acceleration time to ejection time (AT / ET) is a marker of aortic valve stenosis severity (Einarsen *et al*., 2021). In the diagnosis of pulmonary hypertension in dogs and cats, the pulmonary flow pattern changes to resemble the aortic flow pattern. This feature is one of the Doppler findings of pulmonary hypertension (Serres*et al*., 2007).

Propofol is commonly used for the induction and maintenance of anesthesia in both human and veterinary patients. Propofol reduces cardiac output diastolic and systolic blood pressures by causing vasodilation and simultaneously causing a decrease in vascular resistance (Bilotta *et al*., 2001; Larsen *et al*., 2007). Propofol has a dose-dependent myocardial depressive effect in vitro studies (Chen *et al*., 2006; Hamilton *et al*., 2000) but a minimal effect on echocardiographic Doppler parameters in humans (Yang *et al*., 2013) and cats (Ferasin, 2009). Although the effects of sedative and anesthetic drugs on cardiac function and echocardiographic parameters have been investigated in pet and laboratory animals (Baumgartner *et al*., 2010a, b; Marques *et al*., 2020; Farag *et al*., 2022; Sandez *et al*., 2022; Bagardi *et al*., 2023; Marangoni *et al*., 2023; Bitencourt *et al*., 2024; Bockay *et al*., 2024), the effects of propofol on the Doppler echocardiographic values of the aorta and main pulmonary artery and the deceleration time of the mitral E wave (Edec) have not been reported in rabbits.

This study aimed to determine the effect of propofol on aortic and pulmonic AT, ET, and AT / ET and mitral Edec in New Zealand white rabbits.

Materials and Methods

The experimental protocol on the use of animals was approved by the Akdeniz University Animal Care Ethics Committee (No: 1653/2023.11.010/112). All animals were normal based on a physical examination and echocardiography. Rabbits were considered normal if they were free of any murmur, extra heart sounds, arrhythmia, abnormal respiratory sounds on auscultation, and no evidence of any morphologic or hemodynamic cardiac changes on echocardiography such as mitral valve thickening or prolapse, presence of a mitral, tricuspid, aortic or main pulmonary artery regurgitating jet, pericardial or pleural effusion.

Complete echocardiographic examinations, which included transthoracic 2-dimensional (2D), M-mode, and Doppler imaging, were performed by the same observer (MK), more than 20 years' veterinary echocardiography experience, were performed using an ultrasonographic unit (Mindray DC-80, Shenzhen Mindray Bio-medical Electronics, China) equipped with an electronic phased-array sector transducer (8-12 MHz). Echocardiographic parameters were obtained from 40 conscious animals (Group C). Propofol (15 mg/kg, *iv slowly*, Sandoz® İlaç San. Tic. AŞ, İstanbul, Türkiye) was administered to the same animals, and the same echocardiographic parameters were measured within 10 minutes from the beginning of sedation (Group P).

Rabbits were restrained in right and left lateral recumbencies over an opening in an echocardiographic scanning table. An assistant placed the thumb of one hand on the cervicothoracic junction and the other fingers proximal to the elbow joint to direct the forelimbs cranially. The thumb of the other hand was placed just cranial to the iliac crest, and the other fingers proximal to the knee joint to direct the hindlimbs caudally. Thus, the rabbits were restrained. Sonographic images of the heart were obtained by placing the ultrasound probe through this opening into the shaved area from the third to fifth intercostal space on the right side and approximately the fourth intercostal space on the left side.

Echocardiographic measurements were obtained according to previously described in rabbits (Giraldo *et al*., 2019; Turner Giannico *et al*., 2015). M-mode and spectral Doppler measurements were performed by setting the sweep speed to the fastest level. Since the ECG marker was not used during spectral measurements, mitral A wave and E/A ratio were not evaluated. The following measurements and calculations were carried out: on a right parasternal short-axis view (RPSA) at the level of the papillary muscles, 2D guided M-mode of the interventricular septum, left ventricle (LV) posterior wall, LV internal diameter in diastole and systole, and then the LV ejection fraction (EF) and fractional shortening (FS) (EF% and FS% were calculated from measurements for using the internal ultrasound system software) (Fig. 1); on a RPSA at the level of the aortic valve, peak velocity (Vmax), peak pressure gradient (PGmax), acceleration time (AT), ejection time (ET), AT / ET ratio from MPA flow (Fig. 2); on a left sided parasternal apical (LSPA) five-chamber view, Vmax, PGmax, AT, ET, AT / ET ratio from Ao flow (Fig. 3); LSPA four-chamber view, peak velocity of E wave (Vvel), Edec, E duration (Edur) (Fig. 4). The measurement of HR was carried out manually using the echocardiographic software for each loop individually (Fig. 1).

Statistical analysis was carried out on commercial software (IBM SPSS Statistics 22.0, SPSS Inc., USA). Data were expressed as the mean ± standard deviation (SD). A two-sample *t*-test for all echocardiographic

parameters was used to assess the differences between groups. A *P* value < .05 was regarded as statistically significant.

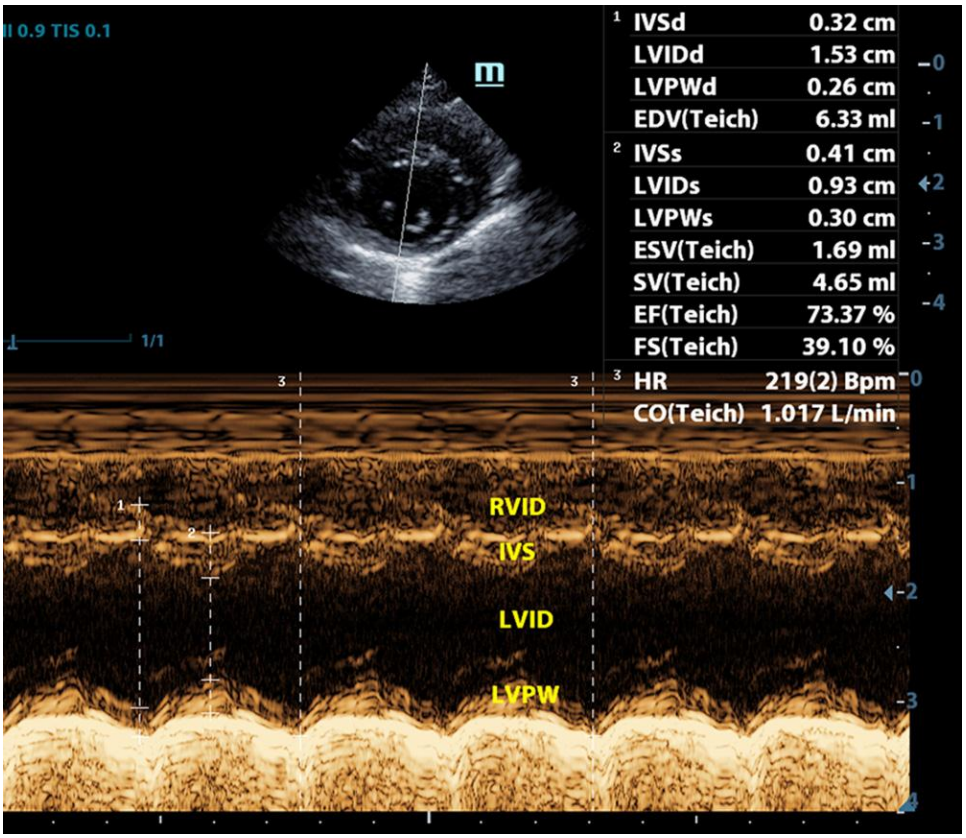

Figure 1 From the right parasternal short axis at the level of papillary muscles, measurement of echocardiographic M-Mode parameters of the left ventricle. RVID: right ventricle internal diameter, IVS: interventricular septum, LVID: left ventricle internal diameter, LVPW: left ventricle posterior wall, EF: ejection fraction, FS: fractional shortening, HR: heart rate, CO: cardiac output.

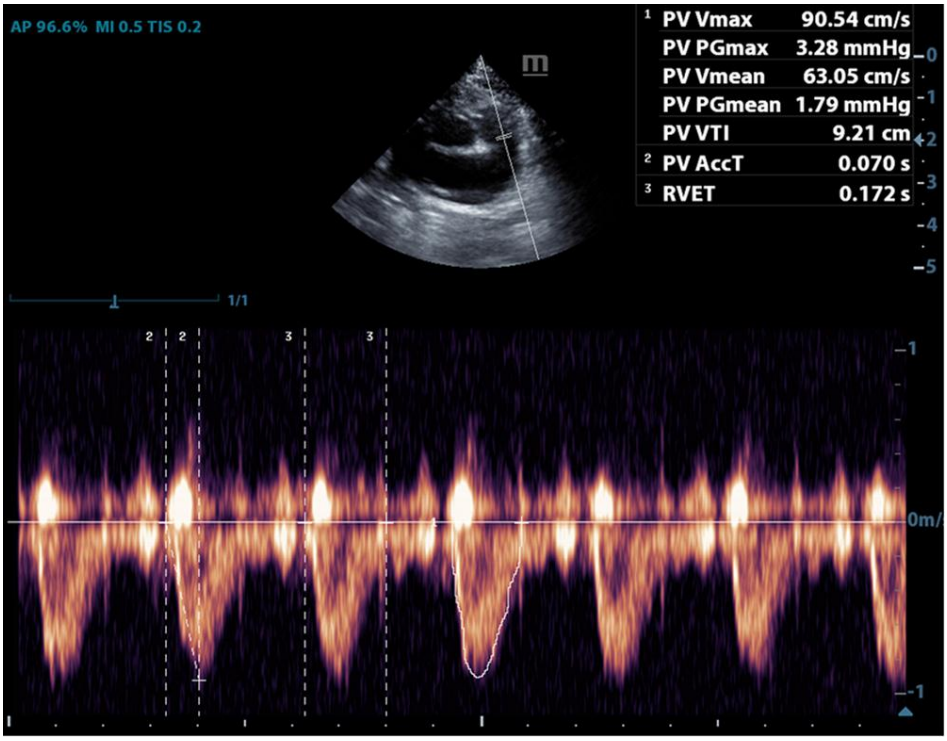

Figure 2 From the right parasternal short axis at the level of the aorta, measurement of echocardiographic Doppler parameters of the main pulmonary artery. Vmax: peak velocity; PGmax: peak pressure gradient; PV AccT: Acceleration time (AT); RVET: right ventricle ejection time (ET). The AT / ET ratio is 0.407 in this rabbit.

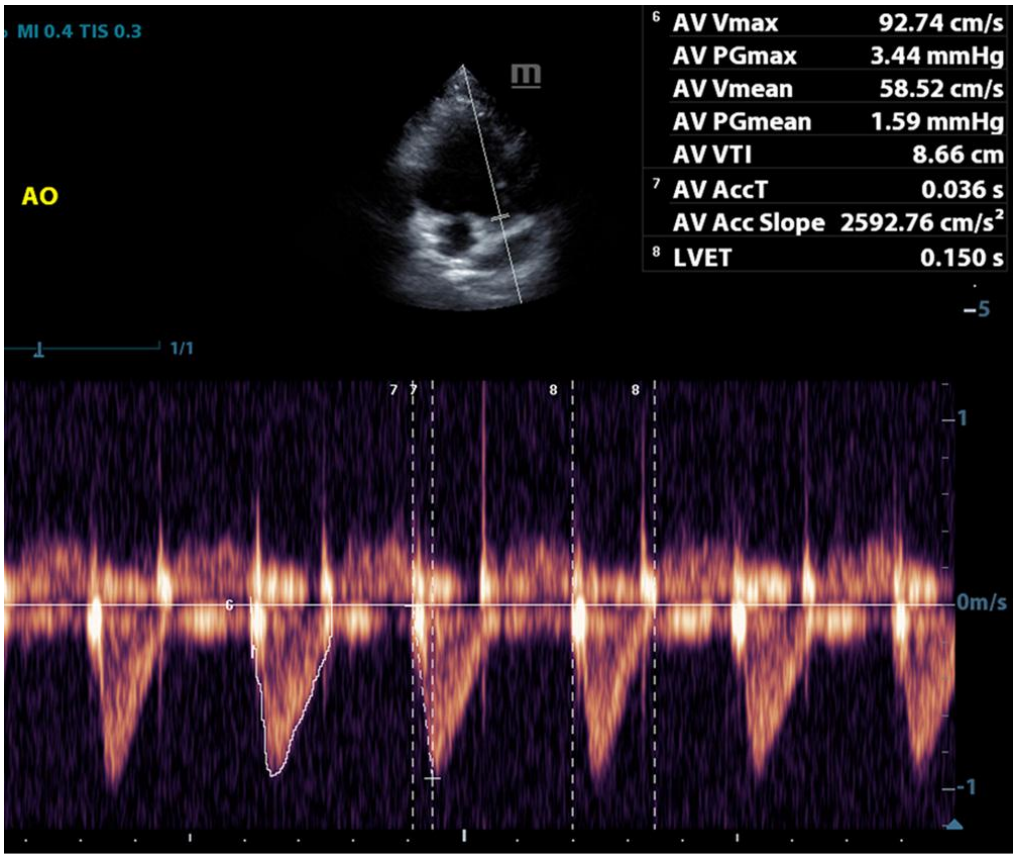

Figure 3 From the left side of the parasternal apical five-chamber view, the echocardiographic Doppler parameters of the aorta are measured. Vmax: peak velocity; PGmax: peak pressure gradient; AV AccT: Acceleration time (AT); LVET: left ventricle ejection time (ET). The AT / ET ratio is 0.24.

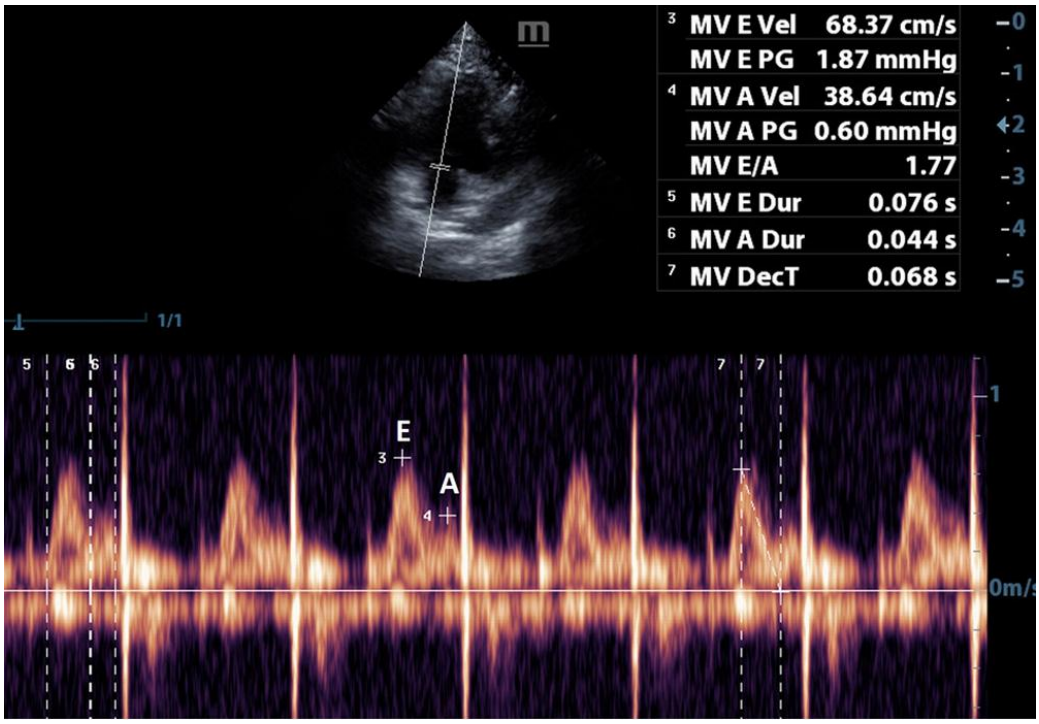

Figure 4 From the left side of the parasternal apical five-chamber view, the echocardiographic Doppler parameters of the mitral flow in a rabbit are measured. E vel: peak velocity of the E wave, E PG: peak pressure gradient of the E wave, E Dur: duration of the E wave, DecT: deceleration time of E wave.

Result

In total, the echocardiographic parameters of 40 conscious and sedated healthy male New Zealand white rabbits were analyzed. Mean age and mean BW were 12.65 ± 1.89 months (10-16 months) and 3.38 ± 0.36 kg (2.7-3.8 kg), respectively. No complications associated with propofol were encountered in any animals, and no mortality occurred.

Table 1 shows the echocardiographic values measured from flows of the aorta and main pulmonary artery in Group C. The HR, EF%, and FS% values were lower in Group P than in Group C ($P < 0.001$, 197.55 ± 18.8 bpm *vs* 239.43 ± 26.62 bpm, 63.2 ± 3.79 *vs* 70.1 ± 4.47, 32.15 ± 2.43 *vs* 37.85 ± 3.74, respectively).

Peak velocities and pressures of Ao were decreased in Group P ($P < 0.05$). While the pulmonic flow pattern was substantially symmetrical (Fig. 2), the aortic flow pattern was asymmetric in Group C (Fig. 3). In both aortic and pulmonic flow patterns, the AT was longer ($P < 0.05$), and thus pulmonic flow pattern became more symmetrical in Group P. The change in the aortic and pulmonic AT/ET was statistically significant ($P < 0.001$) (Table 2).

Administration of propofol did not change the mitral flow pattern. Among Doppler echocardiographic values of the mitral E wave, there was only a statistically significant difference for Edec ($P = 0.008$) (Table 3).

Table 1 Mean, 95% confidence interval (CI), and minimum-maximum values of echocardiographic values from flows of the aorta and main pulmonary artery in 40 conscious New Zealand white rabbits.

Vessel	Parameters	Mean ± SD	95% CI	Range
Ao	Vmax (*cm/s*)	90.76 ± 14.39	86.16-95.36	63.5-127.4
	PGmax (*mmHg*)	3.47 ± 1.01	3.15-3.79	1.61-6.5
	AT (*s*)	0.028 ± 0.006	0.026-0.03	0.018-0.035
	ET (*s*)	0.116 ± 0.017	0.112-0.123	0.096-0.154
	AT/ET	0.23 ± 0.036	0.22-0.25	0.18-0.30
MPA	Vmax (*cm/s*)	83.42 ± 13.29	78.85-87,99	61.3-112.4
	PGmax (*mmHg*)	2.85 ± 0.97	2.54-3.17	1.5-5.05
	AT (*s*)	0.05 ± 0.01	0.049-0.055	0.03-0.07
	ET (*s*)	0.137 ± 0.018	0.131-0.143	0.099-0.174
	AT/ET	0.38 ± 0.037	0.37-0.4	0.33-0.49

Abbreviations: SD, standard deviation; Ao, Aorta; MPA, Main pulmonary artery; Vmax, peak velocity; PGmax, peak pressure gradient; AT, acceleration time; ET, ejection time; AT/ET: ratio of AT to ET.

Table 2 Comparison of Doppler echocardiographic parameters from flows of the aorta and main pulmonary artery between groups.

Vessel	Parameters	Group	Mean ± SD	*P* value
Ao	Vmax (*cm/s*)	C	90.76 ± 14.39	0.044
		P	83.04 ± 12.24	
	PGmax (*mmHg*)	C	3.47 ± 1.01	0.036
		P	2.98 ± 0.77	
	AT (*s*)	C	0.028± 0.006	0.04
		P	0.032 ± 0.005	
	ET (*s*)	C	0.116 ± 0.017	0.208
		P	0.111 ± 0.015	
	AT / ET	C	0.23 ± 0.036	0.001
		P	0.28 ± 0.021	
MPA	Vmax (*cm/s*)	C	83.42 ± 13.29	0.345
		P	79.74 ± 12.74	
	PGmax (*mmHg*)	C	2.85 ± 0.97	0.322
		P	2.6 ± 0.85	
	AT (*s*)	C	0.05 ± 0.001	0.037
		P	0.056 ± 0.007	
	ET (*s*)	C	0.137 ± 0.018	0.639
		P	0.135 ± 0.016	
	AT / ET	C	0.38 ± 0.037	0.001
		P	0.44 ± 0.036	

Abbreviations: SD, standard deviation; CI, confidence interval; C, conscious; P, propofol; Ao, aorta; MPA, main pulmonary artery; Vmax, peak velocity; PGmax, peak pressure gradient; AT, acceleration time; ET, ejection time; AT/ET, the ratio of AT to ET.

Table 3 Comparison of Doppler echocardiographic parameters of the mitral E wave between groups.

Parameters	Group	Mean ± SD	*P* value
Evel (*cm/s*)	C	84.13 ± 18.26	0.054
	P	77.6 ± 15.99	
E PG (*mmHg*)	C	3.06 ± 1.38	0.064
	P	2.69 ± 1.32	
Edur (*s*)	C	0.069± 0.018	0.059
	P	0.06 ± 0.014	
Edec (*s*)	C	0.046 ± 0.015	0.008
	P	0.034 ± 0.009	

Discussion

Based on a review of the literature, this is the first study proposing the reference intervals for AT, ET, and AT / ET from flows of the aorta and main pulmonary artery in NZW rabbits. Aortic AT / ET is a straightforward and reproducible echocardiographic parameter that combines the severity of aortic stenosis with the effects it has on the left ventricle. AT / ET > 0.35 is a strong predictor of outcome in human patients with high-gradient severe aortic stenosis (Altes *et al*., 2021). Pulmonic AT, ET, and AT / ET are used to evaluate both humans and dogs with precapillary pulmonary hypertension (PH). Three different patterns of flow have been described: type I: normal, symmetrical flow pattern; type II: moderate PH, asymmetrical flow pattern; shortened AT; type III, severe PH, furthermore shortened AT and mid-systolic notch in the flow pattern (Atkinson *et al*., 2009; Serres *et al*., 2007). The threshold value for predicting PH in dogs has been reported as pulmonic AT / ET < 0.31 and AT < 0.058 seconds (s) (Schober and Baade, 2006). In a cat with type III reversible pulmonary hypertension, pulmonic AT, ET, and AT / ET have been reported as 0.04 s, 0.133 s, and 0.26, respectively (Baron Toaldo *et al*., 2011). In normal dogs, the aortic flow pattern is typically asymmetric, and AT / ET is lower than 0.3, whereas the pulmonic flow pattern has a more symmetric shape and an AT/ET greater than 0.43 (Kirberger *et al*., 1992). Although the aortic AT / ET in the presented study was consistent with the values obtained in dogs, pulmonic AT / ET was lower than the values in dogs. On the other hand, pulmonic AT / ET (median: 0.37, range: 0.28-0.41) in healthy cats (Lachance *et al*., 2022) is consistent with the findings of this study.

The use of a sedative protocol to reduce stress and facilitate handling in rabbit echocardiography is common, especially in experimental studies. The combination frequently used for this purpose is ketamine-α_2 agonists. This combination has the potential for cardiac and respiratory depression. The combinations of ketamine-midazolam (Fontes-Sousa *et al*., 2009) and dexmedetomidine-midazolam-morphine (Bitencourt *et al*., 2023) have been reported to be associated with minimal cardiorespiratory depression. In low-risk human patients, propofol causes a negligible subclinical reduction in LV systolic and diastolic echocardiographic parameters (Yang *et al*., 2013). Although this anesthetic caused a slight decrease in myocardial systolic velocities, a tissue Doppler study showed that it did not affect diastolic function in cats (Ferasin, 2009). In the presented study, although propofol was effective on LV systolic function parameters (EF% and FS%) and HR, it did not cause systolic dysfunction or bradycardia, and thus its effect appears to be minimal on LV systolic function, as in humans (Freitas *et al*., 2022). In the presented study, the decrease in FS and EF values after propofol administration can be explained by a decrease in cardiac output (Sahinovic *et al*., 2018). Additionally, Doppler echocardiographic values of mitral E wave were not affected, except for Edec. The decrease in both aortic and pulmonary velocities and pressure gradients seen after propofol administration in this study may be due to partial suppression of left ventricular (LV) systolic function (Freitas *et al*., 2022) and a significant decrease in sympathetic tone. (Sahinovic *et al*., 2018). Although the increase in the pulmonic AT / ET makes this flow pattern more symmetrical, it is a situation that should be taken into account in future studies. The mean aortic AT / ET (0.29 ± 0.021) in Group P is a change that should be taken into account, although the fact that it is below the threshold value for human aortic stenosis > 0.35 may also indicate a difference that does not cause adverse effects. Further research is now needed to determine the Doppler echocardiographic diagnostic criteria of aortic stenosis and pulmonary hypertension in rabbits.

As a result, propofol administration may not have any effect on Doppler echocardiographic values of mitral E wave, except for Edec. The effect of propofol on aortic and pulmonic AT / ET, as well as LV systolic function parameters, should be taken into account.

Acknowledgment

The experimental protocol on the use of animals was approved by the Akdeniz University Animal Care Ethics Committee (No: 1653/2023.11.010/112). The authors confirm that they have adhered to ARRIVE Guidelines to protect animals used for scientific purposes.

Conflict of interest: The authors declare no conflict of interest.

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