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Effects of acepromazine maleate and morphine on blood pressure, electrocardiographic parameters, and conventional echocardiographic findings in healthy dogs

Efeitos do maleato de acepromazina e da morfina na pressão sanguínea, eletrocardiografia e ecocardiografia convencional em cães saudáveis

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Highlights

Acepromazine and morphine improves the manageability of dogs during cardiac exams.
In echocardiographic evaluation, acepromazine alone reduces cardiac output.
Acepromazine has milder effects on electrocardiographic parameters in dogs.

Abstract

Electrocardiography and echocardiography are essential tools for the diagnosis, prognosis, and therapeutic management of canine heart diseases, with echocardiography considered the gold standard for several conditions. In some cases, however, chemical restraint is required to perform these examinations due to aggression, stress, or respiratory difficulty. The aim of this study was to assess the cardiovascular effects of sedation with acepromazine alone or combined with morphine in healthy dogs undergoing electrocardiographic and echocardiographic evaluation. Sixteen dogs were randomly allocated into 2 groups: the acepromazine group (AG, n=8), which received 0.2% acepromazine at 0.05 mg/kg intramuscularly, and the acepromazine and morphine group (AMG, n= 8), which received 0.2% acepromazine at 0.05 mg/kg combined with 1% morphine at 0.5 mg/kg, both administered intramuscularly. Before sedation, animals were placed in lateral recumbency for baseline assessment (M0) of electrocardiographic and echocardiographic parameters, as well as systolic, diastolic, and mean blood pressure (SBP, DBP and MAP). The same assessment was repeated 20 minutes after treatment (M1).

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Both groups showed reductions in cardiac output, SBP and MAP. Additional effects were observed in the AMG, including reductions in aortic valve pressure gradient, E-wave peak velocity, heart rate and DBP, together with a prolonged QT interval on the electrocardiogram. In conclusion, both protocols proved effective for chemical restraint. However, acepromazine alone produced only a decrease in cardiac output on echocardiography, while other variables remained relatively stable. Thus, acepromazine alone has a less pronounced effect on electrocardiographic and conventional echocardiographic findings in healthy dogs.
Key words: Cardiac exams. Sedative drugs. Dog.

Resumo

A eletrocardiografia e a ecocardiografia são instrumentos de grande importância no diagnóstico, prognóstico e direcionamento terapêutico das cardiopatias caninas; sendo o ecocardiograma padrão ouro para diversas delas. No entanto, algumas vezes é necessário realizar a contenção química dos animais para se conseguir realizar os exames devido à agressividade, estresse ou angústia respiratória. Assim, o objetivo deste estudo foi avaliar os efeitos cardiovasculares da sedação com acepromazina ou sua associação à morfina na contenção química de cães submetidos a exames eletrocardiográficos e ecocardiográficos. Foram utilizados 16 cães alocados aleatoriamente em dois grupos: grupo acepromazina (GA, n=8) os quais receberam acepromazina a 0,2% na dose de 0,05 mg/kg por via intramuscular e grupo acepromazina e morfina (GAM, n=8) que receberam acepromazina a 0,2% na dose de 0,05 mg/kg associada à morfina 1% na dose de 0,5 mg/kg, ambas por via intramuscular. Previamente à sedação, os animais foram posicionados em decúbito lateral para avaliação basal (M0) dos parâmetros de eletrocardiografia e ecocardiografia; além da aferição da pressão arterial sistólica, diastólica e média (PAS, PAD e PAM). Esta avaliação repetiu-se 20 minutos após a administração dos tratamentos (M1). Verificou-se em ambos os grupos uma redução no débito cardíaco e na PAS e PAM. No GAM, observou-se também uma redução do gradiente de pressão da valva aórtica, da velocidade de pico da onda E, da frequência cardíaca e da PAD, além de um aumento da duração do intervalo QT no eletrocardiograma. Conclui-se que, ambos os protocolos foram eficazes na contenção química dos animais. No entanto, a acepromazina causou, no exame ecocardiográfico convencional, apenas redução do débito cardíaco, permanecendo todas as demais medidas sem alterações significativas. E, a acepromazina, isoladamente, exerceu menor influência sobre a função cardíaca de cães saudáveis visualizada pelas medidas eletrocardiográficas e ecocardiográficas.
Palavras-chave: Exames cardíacos. Drogas sedativas. Cão.

Introduction

The electrocardiogram (ECG) is an essential tool for evaluating cardiac electrical activity and plays a key role in diagnosing and monitoring arrhythmias and conduction disorders. Alterations in ECG waves, intervals, and arrhythmic events are particularly relevant in pharmacological investigations, especially when assessing the safety of therapeutic interventions (Botelho et al., 2019). Echocardiography, the

ultrasound evaluation of the heart and great vessels, is considered the gold standard for diagnosing various cardiac conditions in veterinary medicine. It provides a non-invasive assessment of cardiac anatomy and function, allowing detection of valvular disorders, congenital anomalies, myocardial contractile abnormalities, and pericardial effusion, as well as monitoring treatment response and disease progression (Oyama, 2004; Wess et al., 2017). Nevertheless, echocardiographic findings should be interpreted alongside clinical examination, electrocardiography, thoracic radiography, and other complementary tests for an accurate assessment (Wess, 2022).

Although sedation is not always necessary, it can improve image acquisition by reducing anxiety and movement, thereby enhancing examination quality (Kellihan et al., 2015; Santarelli et al., 2017). An ideal sedative regimen for cardiovascular diagnostics should provide sufficient calmness and immobilization while maintaining stable hemodynamic parameters (Saponaro et al., 2013). Acepromazine, a widely used phenothiazine sedative, reduces stress and excitement during veterinary procedures (Schneiders et al., 2012) and provides effective sedation with minimal cardiorespiratory compromise. It acts by decreasing activity in the reticular activating system and through anti-dopaminergic effects on the central nervous system (Stepien et al., 1995; Cavalcanti et al., 2007; Silva et al., 2008). Combining phenothiazines with opioids is recommended for achieving deep sedation while maintaining cardiorespiratory stability (Mouney et al., 2011). Morphine, a principal opioid analgesic, binds predominantly to μ receptors and modulates nerve activity by promoting potassium efflux or reducing calcium influx in nerve cells (Pasternak, 2005). It induces analgesia, relaxation, and drowsiness via central nervous system effects (Monteiro et al., 2009) and can influence blood pressure and heart rate depending on the administered dose (Hashiguchi et al., 1996).

Given this context, the present study aimed to compare the electrocardiographic and echocardiographic parameters of dogs subjected to two sedation protocols to identify the most suitable approach during these examinations.

Material and Methods

Animals and clinical evaluation

Sixteen healthy, medium-sized adult dogs (mean age: 2 years; both sexes; body condition score: 3/5) from the Lages Zoonosis Control Center were enrolled prior to elective castration. All procedures followed the ethical principles for animal experimentation established by the UDESC Animal Ethics Committee (CETEA 01.14.12).

Before enrollment, each dog underwent a full clinical evaluation including mucous membrane, capillary refill time, heart and respiratory rate, cardiopulmonary auscultation, lymph node palpation, rectal temperature, complete blood count, liver and renal function, blood pressure measurement, electrocardiography, and echocardiography. Dogs with cardiac abnormalities or contraindications to the study protocols were excluded.

Experimental groups / Treatments

Animals were randomly assigned to one of two groups: the acepromazine group (AG, n=8), which received 0.2% acepromazine maleate at 0.05 mg/kg intramuscularly, and the acepromazine and morphine group (AMG, n=8), which received 0.2% acepromazine maleate at 0.05 mg/kg combined with 1% morphine sulfate at 0.5mg/kg, both administered intramuscularly.

Blood pressure

Systolic (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured five times with a digital oscillometric device and an appropriately sized cuff placed around the left forelimb, with dogs positioned in right lateral recumbency.

Electrocardiography

Electrocardiography, echocardiography, and blood pressure assessments were performed at baseline (M0) and 20 minutes after sedation (M1) in both groups.

Electrocardiographic recordings were obtained using a computerized six-channel non-invasive system (TEB®, ECGPC version 2.07, Brazilian Electronic Technology - TEB, São Paulo, SP, Brazil).

Electrodes for limb leads were attached to the skin with metal clips at the humeroradioulnar and femorotibiopatellar joints. Bipolar leads DI, DII and DIII, and unipolar leads aVR, aVL and aVF, were recorded. Paper speed was set at 50 mm/s and calibration at 1mV= 1cm (N). The following were evaluated: heart rate and rhythm, P wave and QRS complex duration (s) and amplitude (mV), PR and QT interval duration (s), ST-segment level, T-wave polarity, and QRS axis. Measurements were obtained from lead II. The QRS axis was determined by summing the positive and negative deflections of leads I and III, following Tilley (1992).

Echocardiography

Two-dimensional (2D), M-mode, and Doppler (pulsed and continuous) echocardiography were performed using a Philips® Affiniti 50 ultrasound system. The right and left thoracic walls were clipped, and gel was applied to improve acoustic coupling. With the dog in right lateral recumbency, the transducer was placed at the right parasternal window (3rd-6th intercostal spaces), allowing acquisition of short- and long-axis views. Long-axis views included the four-chamber and left ventricular outflow tract, while short-axis views were obtained at the apical, papillary, chordal, mitral, and aortic levels (Thomas et al., 1993).

Initial B-mode imaging was used to evaluate chamber anatomy, myocardial contractility, valvular morphology and function, the presence of regurgitant jets on color Doppler, and pulmonary valve pressure gradient. Short-axis views were then used to guide M-mode imaging, displayed simultaneously with two-dimensional views. Measurement included left atrial and aortic diameters, from which the left atrium-to-aorta ratio (LA:Ao) was calculated. Left ventricular diastolic (LVDd) and systolic (LVDs) diameters were measured at the chordae tendineae level, and ejection fraction (Fej) and fractional shortening (FS) were derived.

From the left caudal (apical) parasternal window, in 2D mode, cardiac structural relationships, valve morphology and function, and myocardial contractility were assessed, and the aortic valve pressure gradient (AoPG) was calculated.

Cardiac output was calculated using the modified Simpson's rule (Figure 1), a biplane disk method that estimates left ventricular volume by summing multiple cylindrical disks, thereby minimizing errors related to ventricular geometry (Ciampi & Villari, 2007).

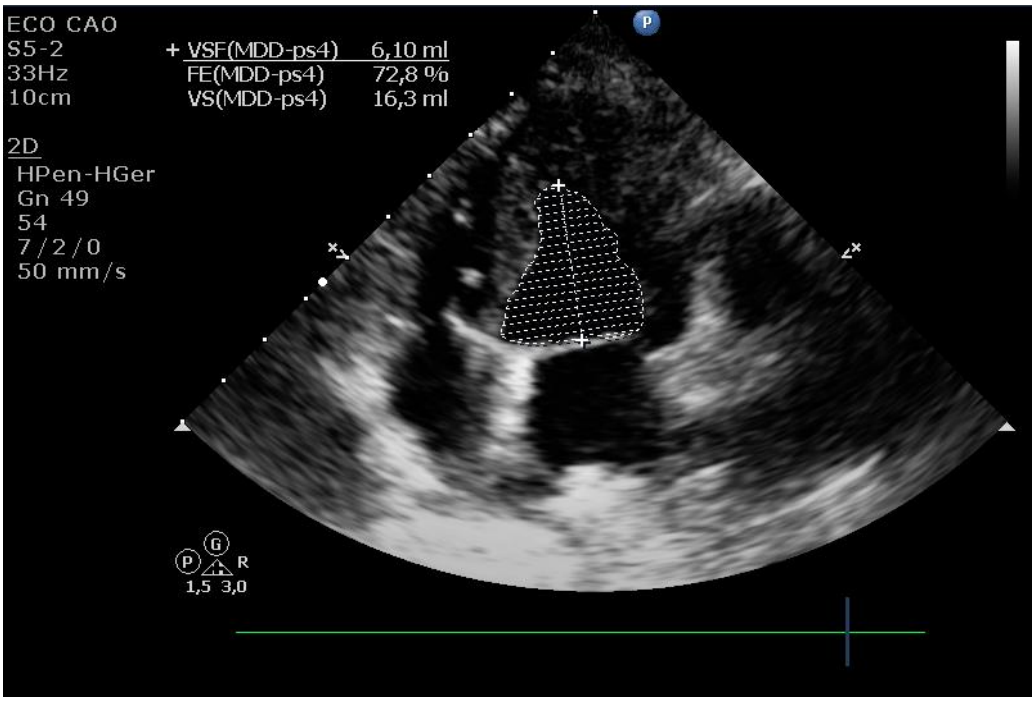

Figure 1. Sizing the volume of the left ventricle in systole to calculate cardiac output using the modified Simpson's rule.

Statistical analysis

For statistical analysis, the cardiac index (CI) was calculated by dividing cardiac output by body weight. Diastolic function was assessed by mitral inflow, measuring E- and A-wave peak velocities and the E/A ratio.

Blood pressure (SBP, DBP, MAP) was measured five times by digital oscillometry, and the mean of the five readings was recorded.

A completely randomized experimental design was applied. Data were analyzed using ANOVA and the Student's t-test, with statistical significance set at $P < 0.05$.

Results and Discussion

Both sedation protocols produced satisfactory results. However, the AMG showed longer-lasting sedation and less movement than the AG. In terms of restraint and sedation duration, both protocols were effective, enabling standard echocardiographic measurements in all 16 dogs during the 15-minute assessment period. Echocardiographic and electrocardiographic image quality also improved in both groups (Figures 2 and 3), which facilitated the acquisition of standard measurements.

Figure 2. Pre-sedation electrocardiogram of a dog (acepromazine and morphine), showing significant baseline interference. Recorded in bipolar lead DII at 25mm/s.

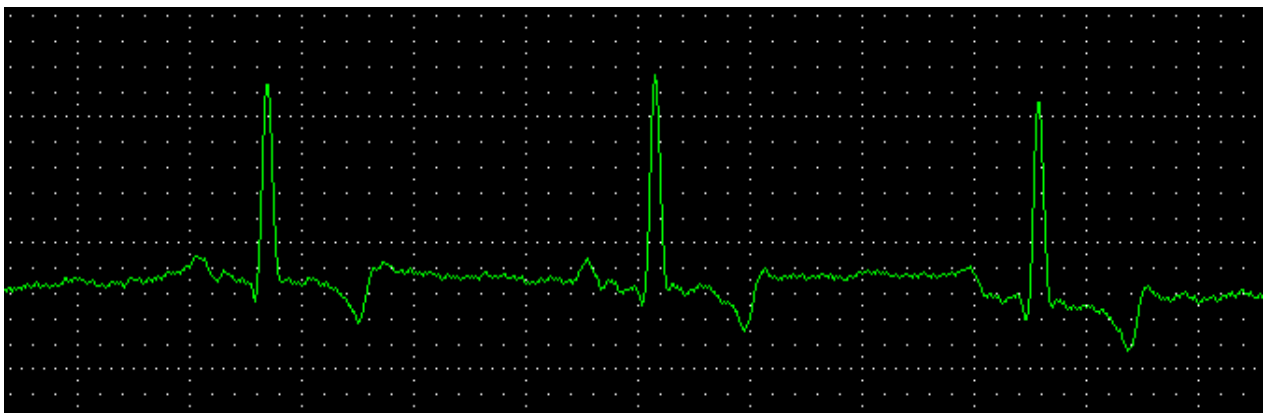

Figure 3. Post-sedation electrocardiogram of a dog (acepromazine and morphine), demonstrating enhanced baseline stability. Recorded in bipolar lead DII at 25mm/s.

Cardiac output, SBP, and MAP decreased in both groups, but only the AMG showed a decline in DBP (Table 1). The only echocardiographic alteration observed in the AG was reduced cardiac output, while all other parameters remained relatively stable (P>0.05). By contrast, the AMG exhibited additional reductions in AoPG and E-wave peak velocity (Table 1).

Significant intergroup differences (P<0.05) were detected in E-wave peak velocity before and after treatment, although AMG values remained higher at both time points. The AMG also showed a higher E/A ratio post-treatment.

Table 1
Echocardiographic parameters (mean±SD) in dogs sedated with acepromazine (AG, (n=8) and acepromazine + morphine (AMG, n=8), before and after treatment. LA/Ao: left atrium-to-aorta ratio; EF: ejection fraction; FS: fractional shortening; AoPG: aortic valve mean pressure gradient; CI: cardiac index; E: early diastolic transmitral flow velocity (E wave peak velocity); A: late diastolic (atrial) flow velocity (A wave peak velocity); E/A: ratio of E to A velocities. Values marked with (') correspond to post-treatment measurements

GROUP	LA/Ao	LA/Ao	EF(%)	EF'(%)	FS(%)	FS'(%)	AoPG (mmHg)	AoPG' (mmHg)
AG	1.202 ± 0.110	1.166 ± 0.140	74.15 ± 8.170	69.28 ± 12.110	42.65 ± 7.020	38.51 ± 8.540	4.00 ± 0.770	3.07 ± 1.080
AMG	1.153 ± 0.134	1.172 ± 0.059	68.86 ± 5.851	66.125 ± 12.704	38.31 ± 4.240	36.63 ± 10.060	4.64* ± 1.050	3.275* ± 1.162
GROUP	CI	CI'	E(cm/s)	E'(cm/s)	A(cm/s)	A'(cm/s)	E/A	E/A'
AG	0.169* ± 0.064	0.116* ± 0.041	83.51# ± 16.44	66.425# ± 18.998	59.627 ± 16.080	46.625 ± 14.252	1.455 ± 0.365	1.782# ± 0.325
AMG	0.176* ± 0.065	0.121* ± 0.022	109.85*# ± 23.49	88.61*# ± 20.23	59.825 ± 28.602	38.825 ± 9.936	1.667 ± 0.455	2.358# ± 0.593

*P < 0.05 vs. pre-treatment within the same group; #P < 0.05 vs. the AG.

Heart rate decreased significantly (p<0.05) from M0 to M1 only in AMG animals (Table 3), with no significant change observed in the AG (P>0.05). On electrocardiography, QT interval prolongation was evident in the AMG (Table 2).

Table 2
Electrocardiographic parameters (mean±SD) in dogs sedated with acepromazine (AG, (n=8) and acepromazine + morphine group (AMg, (n=8), before and after treatment. P(s): P wave duration in seconds; P(mV): P wave amplitude in millivolts; QRS(s): QRS complex duration in seconds; QRS (mV): QRS complex amplitude in millivolts; PR(s): PR interval in seconds; QT(s): QT interval in seconds; Axis: QRS electrical axis in degrees. Post-treatment values are indicated with (').

GROUP	P(s)	P(s)'	P(mV)	P(mV)'	QRS(s)	QRS(s)'	QRS(mV)
AG	0.04 ± 0.003	0.04 ± 0.004	0.176 ± 0.086	0.182 ± 0.102	0.035 ± 0.005	0.033 ± 0.003	0.956 ± 0.471
AMG	0.041 ± 0.005	0.042 ± 0.002	0.196 ± 0.095	0.155 ± 0.061	0.036 ± 0.003	0.037 ± 0.003	1.325 ± 0.220
GROUP	QRS(mV)'	PR(s)	PR(s)'	QT(s)	QT(s)'	Axis	Axis'
AG	0.861 ± 0.384	0.105 ± 0.008	0.104 ± 0.013	0.17 ± 0.039	0.201 ± 0.019	75 ± 12.32	75 ± 18.30
AMG	1.205 ± 0.243	0.105 ± 0.007	0.111 ± 0.008	0.164* ± 0.027	0.217* ± 0.026	67 ± 5.17	67 ± 9.01

*P< 0.05 vs. pre-treatment within the same group; #P < 0.05 vs. the AG.

The decreases in in SBP and MAP are consistent with the vasodilatory effects of phenothiazines, which are amplified when combined with opioids (Table 3). Acepromazine maleate, a phenothiazine tranquilizer, reduces arousal and motor activity primarily through dopaminergic antagonism (Stepien et al., 1995), and its alpha-adrenergic blocking effect contributes to hypotension (Monteiro et al., 2009; Rangel et al., 2020). Similar results were reported by Cavalcanti et al. (2007) in Boxer dogs sedated with 0.03mg/kg of intravenous acepromazine.

Table 3
Blood pressure and heart rate (mean±SD) in dogs sedated with acepromazine (AG, (n=8) and acepromazine + morphine (AMG, (n=8), before and after treatment. SBP: systolic blood pressure (mmHg); MAP: mean arterial pressure (mmHg); DBP: diastolic blood pressure (mmHg); HR: heart rate (bpm). Post-treatment values are indicated with (').

GROUP	SBP	SBP'	MAP	MAP'	DBP	DBP'	HR	HR'
GA	160* ± 7,21	140* ± 16,56	112* ± 4,99	97* ± 12,34	86 ± 6,75	77 ± 13,61	128 ± 24,28	123 ± 32,37
GAM	171* ± 19,96	132* ± 24,84	116* ± 14,82	88* ± 18,12	92* ± 12,26	68* ± 15,31	140* ± 18,10	101* ± 29,97

*P < 0.05 vs. pre-treatment within the same group; #P < 0.05 vs. the AG.

Although no significant differences in SBP, MAP, or DBP were observed between the AG and AMG (P<0.05), morphine can trigger histamine release via mast cell degranulation, which contributes to hypotension. Although the precise mechanism remains unclear, intramuscular or subcutaneous administration helps minimize these effects (Veien et al., 2000; Guedes et al., 2006; Schmidt-Rondon et al., 2018; Shepherd, 2003).

The significant HR reduction observed in the AMG (P < 0.05) may be explained by opioid peptide receptors in the heart, which influence cardiovascular reflexes through central mechanisms (Barron, 1999). Morphine alters blood pressure and HR in a dose-dependent manner (Hashiguchi et al., 1996). Opioid peptides and their G protein-coupled receptors are important modulators of cardiovascular function, influencing electrophysiology, HR, myocardial contractility, and vascular tone (Headrick et al., 2012). Activation of peripheral opioid receptors may mediate some cardiovascular effects, while others result from direct or independent actions in cardiac tissue and the peripheral vasculature. Among the three main receptor types, (μ, κ and δ) and their pharmacological subtypes (Skiba et al., 2024), κ-agonists contribute to sympathetic cardiac activation, whereas μ-agonists significantly depress baroreflexes and induce bradycardia (Lishmanov et al., 1999).

In addition to HR reduction, AMG dogs exhibited QT interval prolongation. The QT interval represents the time required for ventricular depolarization and repolarization, that is, the duration of ventricular electrical activity (Botelho et al., 2019). Because it varies inversely with HR, this interval is commonly corrected for HR (QTc) to provide a more reliable index.

In human medicine, QT dispersion is a recognized marker of ventricular repolarization heterogeneity and arrhythmogenesis (Shimoni et al., 1995). Prolonged QT has been linked to increased risk of sudden death (Sawicki et al., 1998; Christensen et al., 2000) and is considered a prognostic indicator in heart failure and

hypertrophic cardiomyopathy (Day et al., 1990; Dritsas et al., 1992).

Echocardiographic evaluation revealed a significant reduction ($p<0.05$) in cardiac index following drug administration, indicating decreased cardiac output. Cardiac output depends on HR determined by sinoatrial node depolarization rate and modulated by the autonomic nervous system and stroke volume, which is influenced by preload, afterload, and contractility (Messerer et al., 2012). In the AG, the α-adrenergic action of acepromazine maleate (Tranquilli et al., 2007) reduced preload, thereby lowering cardiac output. In the AMG, preload reduction was compounded by a decreased HR, further reducing cardiac output (Messerer et al., 2012).

In the AMG, E wave peak velocity decreased after acepromazine–morphine administration, reflecting delayed ventricular relaxation and mild impairment of diastolic function. Nevertheless, values remained within species-appropriate reference ranges. The E/A ratio also remained positive and within normal limits (Oyama, 2004).

The AMG exhibited a significant reduction ($p<0.05$) in mean AoPG. This likely resulted from decreased HR and cardiac output, in addition to peripheral vasodilation induced by acepromazine and morphine, which together lowered vascular resistance (Shepherd, 2003).

Intergroup comparisons showed significant differences ($p<0.05$) in E wave (E), E´ wave (E') and E/A ratio, with the AMG displaying higher post-administration (M1) values. Despite these shifts, values in both groups remained within normal species ranges (Gentile-Solomon & Abbott, 2016; Visser, 2017).

Previous studies reported similar outcomes. Cavalcanti et al. (2007) and Silva et al. (2008) found that intravenous acepromazine (0.03 mg/kg) reduces canine anxiety without markedly affecting echocardiographic indices. By contrast, the present study's AG exhibited a significant cardiac index increase ($P<0.05$), attributable to reduced preload (Messerer et al., 2012).

Santarelli et al. (2017) demonstrated that a sedative profile combining acepromazine (0.02 mg/kg) and butorphanol (0.2 mg/kg) provided adequate immobilization for echocardiography. Post-sedation, HR, MAP, and SBP fell significantly, aligning with our findings. Conventional echocardiographic variables also shifted after sedation, including reductions in end-diastolic left ventricular volume index, late-diastolic transmitral peak flow velocity, and late-diastolic septal tricuspid and mitral annular velocities; and increases in ejection time and mitral E/A ratio. Global strain remained stable, while segmental strain at the apical lateral wall decreased significantly. The authors concluded that this protocol ensures effective sedation with only minor effects on conventional and speckle-tracking echocardiography.

Conclusions

Both acepromazine alone and acepromazine-morphine achieved effective sedation without major alterations in electrocardiographic and echocardiographic parameters. Nonetheless, acepromazine appears preferable, since it minimized cardiovascular impact while providing adequate sedation.

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