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EFEITO DA CLONIDINA SOBRE A VARIABILIDADE DA FREQUÊNCIA CARDÍACA EM CÃES ANESTESIADOS

FERNANDA MELO DE OLIVEIRA

DISSERTAÇÃO DE MESTRADO

Uruguaiana, Rio Grande do Sul, 2021.

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Dissertação apresentada ao programa de Pós graduação Stricto sensu em Ciência Animal da Universidade Federal do Pampa, como requisito parcial para obtenção do Título de Mestre em Ciência Animal.

Orientador: Prof. Dr. João Paulo da Exaltação Pascon.

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LISTA DE ABREVIATURA E SIGLAS

μ - Mi
(+) - Positivo
(-) – Negativo
> - maior
ºC – graus Celsius
CLG – Grupo Clonidina
CG – Grupo Controle
μg- microgramas
CAM – Concetração alveolar mínima
FC – Frequência Cardíaca
f – frequência respiratória
h – Hora
IV – Intravenoso
kg – quilogramas
mL – mililitros
min – minutos
mg - miligramas
mm – milímetros
mmHg - milímetros de mercúrio
mmol/L – milimols por litro
MPA – medicação pré-anestésica
PA – Pressão arterial
PAD – Pressão Arterial Diastólica
PAM – Pressão Arterial Média
PN > 50 - Percentagem de Intervalos Consecutivos com Diferença Superior a 50ms
PAS – Pressão Arterial Sistólica
RMSSD – Raiz Quadrada (genérica).
SNC – Sistema Nervoso central
SNP – Sistema Nervoso Parassimpático
SDNN – Desvio Padrão
VFC - Variabilidade da Frequência Cardíaca

SUMÁRIO

RESUMO

A clonidina é um fármaco agonista alfa-2 adrenérgico, com novo potencial de utilização como medicação pré-anestésica em cães com problemas comportamentais baseados no medo, devido ao seu efeito atenuante sobre o sistema nervoso autonômico simpático. No entanto, os riscos associados aos efeitos autonômicos cardíacos e hemodinâmicos da clonidina, bem como de sua associação a outros fármacos do protocolo anestésico devem ser considerados. Nesse contexto, o objetivo deste estudo foi avaliar os efeitos do uso pré-anestésico de clonidina (5µg.kg-1), na variabilidade da frequência cardíaca no domínio do tempo e na pressão arterial em cães saudáveis anestesiados. Seis cães adultos saudáveis, sem raça definida, foram submetidos há ambos os protocolos anestésicos: com clonidina (GCL – grupo clonidina) e com solução salina (GC – grupos controle), associados ao propofol (8mg/kg), isoflurano (1CAM), bôlus (2mg/kg) e infusão contínua (1,5mg/kg/h) de tramadol. A variabilidade da frequência cardíaca (VFC) no domínio do tempo e a pressão arterial (sistólica, média e diastólica) foram avaliadas ao longo do tempo. Todas as variáveis de VFC foram maiores no CLG (tempo total de anestesia), principalmente quando associadas ao bôlus de tramadol (T4), infusão contínua (T8) e tempo de extubação traqueal (T10). Não foram observadas diferenças importantes na pressão arterial, mas dois cães apresentaram bloqueio atrioventricular de segundo grau (Mobitz II) no tempo de bôlus de tramadol (T4). Assim, a clonidina aumenta as variáveis da VFC no domínio do tempo, pelo bloqueio do tônus autonômico simpático e aumento do parassimpático, acentuado pelo efeito sinérgico autonômico do tramadol, resultando em distúrbio elétrico cardíaco, que desencoraja essa associação (clonidina e tramadol) em protocolos anestésicos para cães com problemas comportamentais baseados no medo.

Palavra-chave: Problemas comportamentais baseados nomedo, bloqueio atrioventricular, espécie canina, agonista alfa-2

ABSTRACT

Clonidine is an alpha-2 adrenergic agonist with new potential application as a pre-anesthetic medication for a fear-based behavioral problem dogs, due to the attenuation on sympathetic nervous system effect. However, the risks associate to de cardiac autonomic and hemodynamic effects of clonidine, and its association with other drugs should be considered. In this context, the aim of this study was evaluate the effects of the pre-anesthetic use of clonidine (5μg.kg^{-1}), on time domain heart rate variability, and arterial blood pressure in anesthetized healthy dogs. Six healthy mixed-breed, adult dogs were submitted to both clonidine (CLG) and placebo control (CG) anesthetic protocol, associated to propofol (8mg.kg^{-1}), isoflurane (1CAM), tramadol bolus (2mg.kg^{-1}), and continuous infused (1.5mg.kg^{-1}.h). Time domain heart rate variability (HRV) and arterial blood pressure (systolic, mean, and diastolic) was evaluated along the time. All time domain HRV variables were higher on CLG (total time of anesthesia), especially when associated with tramadol bolus (T4), continuous infusion (T8), and on tracheal extubation time (T10). No important differences were observed on arterial blood pressure, but two dogs presented second-degree atrioventricular block (Mobitz II) in the tramadol bolus time (T4). Thus, clonidine increases the time domain HRV by sympathetic outflow block and rise on parasympathetic tonus, accentuated by the autonomic synergic effect of tramadol, resulting in cardiac electrical disturbance, which discourage this association (clonidine and tramadol) in anesthetic protocols for dogs with fear-based behavioral problems.

Keywords: fear-based behavioural problem, atrioventricular block, canine, alpha-2 agonist

1. INTRODUÇÃO

A clonidina é um fármaco agonista alfa-2 que apresenta potente atividade vasoconstritora, sendo utilizado inicialmente como descongestionante nasal, porém foram detectados efeitos colaterais como hipotensão arterial, sedação e bradicardia. A partir disso, iniciou seu uso no tratamento de hipertensão em humanos, no entanto, na medicina veterinária, seu uso teve sucesso para tratar cães com problemas comportamentais baseados no medo, como ansiedade de separação, fobia de tempestade, fobia de ruído e agressão ao medo, reduzindo seus medos ou respostas agressivas desses cães (SINN, 2018; OGATA & DODMAN, 2011), abrindo novos rumos para o uso da clonidina como medicação pré-anestésica para este grupo de cães.

Seu mecanismo de ação pode ser classificado como periférica e central, promovendo a ativação dos α- adrenoceptores pré-sinápticos, nas terminações nervosas periféricas, inibindo a exocitose da noradrenalina, explicando, o efeito de hipotensão e bradicardia. No entanto, a ativação dos receptores α2 pós-sinápticos, na musculatura lisa dos vasos sanguíneos arteriais e venosos, produz vasoconstricção, já no SNC o centro vasomotor diminui o tônus simpático, diminuindo as catecolaminas circulantes, com potencialização da atividade nervosa parassimpática, induzindo, dessa forma, redução na pressão arterial (ALVES et al., 2000).

No sistema cardiovascular tem ação diminuindo as descargas nas fibras pré-ganglionares simpáticas do nervo esplâncnico, bem como nas fibras pós-ganglionares dos nervos cardíacos. Estimulando assim, o tônus parassimpático, contribuindo para redução da frequência cardíaca em consequência do aumento do tônus vagal e da diminuição do impulso simpático. Os estudos hemodinâmicos realizados indicam que a redução de pressão arterial pela clonidina decorre de uma diminuição do débito cardíaco, devido à frequência cardíaca diminuída e ao relaxamento dos vasos de capacitância, com redução da resistência vascular periférica (BENOWITZ, 2006).

Contudo, o uso anestésico da clonidina, pode interferir na influência autonômica quando relacionada à dose, e protocolo aplicado (FERREIRA DA CRUZ, et al., 2011), seus efeitos farmacológicos podem ser avaliados através do método de análise da variabilidade da frequência cardíaca, na qual observa as mudanças no intervalo ou distância entre um batimento e outro. Este intervalo é altamente variável dentro de um determinado período de tempo. A frequência intrínseca de despolarização cardíaca é modulada pelos sistemas nervosos autônomos simpático (SNS) e parassimpático (SNP), que proporcionam homeostase em diferentes situações cotidianas (VANDERLEI et al., 2009). O método consiste em um

estudo não-invasivo de importante utilidade clínica para avaliar a integridade da função neurocardíaca e identificar a importância relativa da regulação simpática e da parassimpática no diagnóstico de doenças cardíacas e do sistema nervoso autônomo (VANDERLEI et al., 2009). As variáveis são obtidas no registro de eletrocardiograma na qual determinar a duração dos intervalos entre complexos QRS normais, são representadas por valor médio dos intervalos NN (NN médio), desvio padrão entre todos os intervalos RR (SDNN), raiz quadrada da média entre as diferenças ao quadrado dos intervalos NN consecutivos (rMSSD) e percentagem de intervalos consecutivos com diferença superior a 50 ms (pNN50). Sendo assim, a frequência cardíaca é calculada em cada ponto no tempo ou nos intervalos entre os complexos sucessivos (PATTANAPON et al., 2018*).*

Assim, com o objetivo de avaliar a viabilidade do uso da clonidina em protocolos anestésicos para cães com problemas comportamentais baseados no medo, este estudo tem como objetivo analisar os efeitos do uso de clonidina como pré-medicação intramuscular na dose de 5µg.kg-1, no domínio do tempo VFC e arterial pressão arterial de cães saudáveis anestesiados.

2. ARTIGO CIENTÍFICO

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AUTONOMIC AND HEMODYNAMIC EFFECTS OF PRE-ANESTHETIC USE OF CLONIDINE IN HEALTHY DOGS

ABSTRACT

Clonidine is an alpha-2 adrenergic agonist with new potential application as a pre-anesthetic medication for a fear-based behavioral problem dogs, due to the attenuation on sympathetic nervous system effect. However, the risks associate to de cardiac autonomic and hemodynamic effects of clonidine, and its association with other drugs should be considered. In this context, the aim of this study was evaluate the effects of the pre-anesthetic use of clonidine (5μg.kg^{-1}), on time domain heart rate variability, and arterial blood pressure in anesthetized healthy dogs. Six healthy mixed-breed, adult dogs were submitted to both clonidine (CLG) and placebo control (CG) anesthetic protocol, associated to propofol (8mg.kg^{-1}), isoflurane (1CAM), tramadol bolus (2mg.kg^{-1}), and continuous infused (1.5mg.kg^{-1}.h). Time domain heart rate variability (HRV) and arterial blood pressure (systolic, mean, and diastolic) was evaluated along the time. All time domain HRV variables were higher on CLG (total time of anesthesia), especially when associated with tramadol bolus (T4), continuous infusion (T8), and on tracheal extubation time (T10). No important differences were observed on arterial blood pressure, but two dogs presented second-degree atrioventricular block (Mobitz II) in the tramadol bolus time (T4). Thus, clonidine increases the time domain HRV by sympathetic outflow block and rise on parasympathetic tonus, accentuated by the autonomic synergic effect of tramadol, resulting in cardiac electrical disturbance, which

discourage this association (clonidine and tramadol) in anesthetic protocols for dogs with fear-based behavioral problems.

Keywords: fear-based behavioural problem, atrioventricular block, canine, alpha-2 agonist

2.1. INTRODUCTION

Clonidine is an alpha-2 adrenergic agonist extensively used in anesthesia and intensive care for human patients (LEINO et al. 2020), especially for its analgesic, and hypotensive effects (SMANIA & GARCIA, 2005). In dogs, clonidine can improve or prolong analgesia, and reduce the required amount of anesthetic drugs during surgical procedures (DEROSSI et al., 2007; NATALINI et al., 2011), which hypothetically would only increase anesthetic safety. However, some autonomic alpha-2 agonist cardiovascular effects such as hypotension, bradycardia, and atrioventricular block, mediated through multiple sites of action, may limit its frequent use in anesthetic protocols of all dogs (NGUYEN et al., 2017; SINCLAIR, 2003).

However, the success use of clonidine to treat dogs with fear-based behavioral problems, such as separation anxiety, storm phobia, noise phobia, and fear aggression, reducing its fears or aggressive responses from these dogs (SINN, 2018; OGATA & DODMAN, 2011), opens new directions for use of clonidine as pre-anesthetic medication for this group of dogs. The behavioral effects of clonidine are related to the action on presynaptic alpha-2 brainstem receptors, resulting in decrease in sympathetic tone by norepinephrine release inhibition, also associated with sedation, analgesia, and anesthesia (OGATA & DODMAN, 2011).

The brain effect of attenuating the sympathetic outflow also results in vasodilatation and hypotension (HYSEK et al., 2012; MITCHELL et al., 2005). Otherwise, the vascular action of the alpha-2 agonist can counteract the hypotensive status by the vasoconstriction effect, but it can also increase the heart parasympathetic influence mediated by barorreflex

mechanism (LEINO et al. 2020). As a nonselective alpha-2 agonist, clonidine can bind to alpha-2A, 2B, and 2C adrenergic receptors and imidazoline receptor, which can influence the autonomic balance of the heart by central or peripheral mechanisms (SINN, 2018). In a peripheral way, clonidine can also decrease the catecholamine discharge in postganglionic sympathetic cardiac nerves, decreasing the heart rate (MAZE & TRANQUILLI, 1991).

Therefore, is expected that clonidine interfere in a heart autonomic balance, however, these many ways of action associated to the interaction effects with other anesthetic drugs, turn it difficult to predict. During anesthetic use of clonidine, the autonomic influence seems to be dose related, and should be evaluated according to applied protocol (FERREIRA DA CRUZ, et al., 2011), to find the best combination of behavioral (SINN, 2018) and heart protection by a sympathetic attenuation (ZHANG & CHENG, 2000; READ, et al., 2014), and minimal deleterious hemodynamic consequences (PATTANAPON et al., 2018).

In this context, heart rate variability (HRV) stands out for being an important, indirect, and non-invasive clinical tool to quantify the cardiac autonomic regulation, applied in many situations for human patients (VANDERLEI et al., 2009), and also tested in anesthetic protocols for dogs (PATTANAPON et al., 2018). The time domain HRV is based on measuring the variation on R-R intervals of normal beats (N-N interval), registered by a surface electrocardiogram, which reflect the autonomic cardiac balance (DOXEY & BOSWOOD, 2004; RASMUSSEN, et al., 2012; BILLMAN, 2013).

Thus, to evaluate the feasibility of the use of clonidine in anesthetic protocols for dogs with fear-based behavioral problems, this study aims to analyze the effects of intramuscular premedication use of clonidine at 5µg.kg^{-1} dose, on time domain HRV and arterial blood pressure of anesthetized healthy dogs.

2.2. MATERIALS AND METHODS

Six mixed breed, no-neutered healthy dogs, including males (n=3) and females (n=3), with body weight ranging from 11.6 to 19kg , and age ranging from 2 to 6 six year old, were enrolled in this study. The dogs came from teaching veterinary hospital of Pampa Federal University (Brazil), and its use in this study was approved by the animal ethics committee (protocol 004/2013) of the same university. The health status of the dogs was verified by physical and hematological evaluation (complete blood count, serum creatinine levels, urea, and liver enzymes alanine aminotransferase and alkaline phosphatase), without clinical evidence of fear-based behavioral problems.

All animals were randomly anesthetized with clonidine (CLG – clonidine group) and placebo (CG – control group) protocols of premedication (paired study), without the knowledge of the evaluators (blind study), respecting 30 days of interval between each procedure. The enrolled dogs were submitted to 12 hours of fasting period before receive premedication with 1 ml of saline solution (NaCl 0,9%) in CG or clonidine at $5\mu g.kg^{-1}$ diluted up to 1ml with saline solution in CLG, both intramuscularly. Anesthetic induction was held with propofol at a dose of $8mg.kg^{-1}$, 15 minutes after premedication, by a cephalic vein access. Animals were intubated with endotracheal tube of appropriate size and kept under spontaneous ventilation. Isoflurane at 1 MAC (approximately 1,41%) was performed to maintain the anesthesia, and an intravascular bolus of 2 $mg.kg^{-1}$ of tramadol hydrochloride was continuously infused at rate of $1.5ml.kg.h^{-1}$ in both groups.

To infer the hemodynamic and heart autonomic effect of the clonidine, the time domain HRV, heart rate, and arterial blood pressure were monitored. Three channels digital holter (Cardiolight® - Cardios Systems Ltda, São Paulo, Brazil) recorded the dogs electrocardiograms (ECG), as described by Calvert (1998), and the time domain HRV variables were obtained by analysis and editing the ECG records by the same experienced

evaluator, using specific software (CardioManenger® CS550 - Cardios Systems Ltda, São Paulo, Brazil). Premature complexes, and their previous and subsequent complexes were excluded for the calculation of the variables, MeanNN (average of all regular R-R (NN) intervals), SDNN (standard deviation (SD) of all regular NN intervals), SDANN (SD of 5-minutes average NN intervals), SDNNi (Mean of the SD of all NN intervals for all 5-minute segments), rMSSD (Square root of the mean of the squares of successive NN interval differences) and pNN >50 (the percentage of intervals longer than 50 ms different from preceding interval).

Electrocardiographic recording of all dogs was started 20 minutes before premedication and finalized after tracheal extubation. The analysis of HRV in time domain was held at total period of electrocardiographic recording, and in five minutes of record at T0 (before the administration of premedication - basal), T1 (after premedication, immediately before application of propofol), T2 (immediately after the beginning of induction with propofol), T3 (after vaporization of isoflurane immediately before the bolus tramadol), T4 (beginning of application of tramadol bolus), T5 (10 minutes after T4), T6 (20 minutes T4), T7 (30 minutes after T4), T8 (40 minutes after T4), T9 (50 minutes after T4) and T10 (immediately before the extubation).

The invasive arterial systolic (SAP), diastolic (DAP), and mean (MAP) blood pressure, obtained by pedal artery catheterization, and recorded every 10 minutes after tramadol infusion beginning, during 60 minutes, in a multiparameter monitor (LW6000 – Digicare Biomedical Technology Inc., Florida, USA).

Considering the total time of evaluation, the average values of time domain HRV (MeanNN, SDNN, SDANN, SDNNi, rMSSD, pNN> 50), and heart rate (maximum, average and minimum) were compared between the CG and CLG groups by paired *t* test ($p < 0.05$). In turn, the averages variables: MeanNN, SDNN, rMSSD, and pNN> 50 of the moments (T0 to

T10), and SAP, MAP, and DAP at each evaluated time (zero, 10, 20, 30, 40, 50, and 60 minutes) were subjected to analysis of variance (ANOVA) for repeated averages over time and compared between the CG and CLC groups within each moment by Bonferroni test ($p < 0.05$). All analyses were performed in statistical software (GraphPad Prism v.5.04, California, USA).

2.3.RESULTS AND DISCUSSION

Considering total time of evaluation, the average variables of time domain HRV MeanNN, SDNN, SDANN, SDNNi, and rMSSD were higher in the CLG ($p<0.05$) when compared with CG (table 1). Additionally, the minimum and average heart rates were lower in the clonidine group (table 1). These findings suggest that intramuscular clonidine premedication at a dose of 5µg.kg-1 results in decreased sympathetic tone and also increased parasympathetic tone over the heart.

Some HRV time domains index like MeanNN, SDNN, SDANN, and SDNNi can be influenced in an indistinctly way by sympathetic and parasympathetic tonus (KHAN et al., 1999; TALKE, 2000). However, the increase on rMSSD is strongly suggestive of the increment of parasympathetic heart influence (BILLMAN, 2013) of clonidine (CLG). This parasympathetic influence was already attributed to a direct central parasympathetic outflow effect of a clonidine in mice (TANK et al., 2004), and humans (GIRGIS et al., 1998; MICHALOUDIS et al., 1998).

During the first minute of the tramadol bolus (T4), an important autonomic synergic effect with the clonidine was observed in CLG, demonstrated by the increase in meanNN variable (table 2, figure 1), and occurrence of second-degree atrioventricular block (Mobitz II) in two dogs. Tramadol is a synthetic opioid widely used for analgesia in dogs acting by different mechanisms, including the reduction of neuronal uptake of norepinephrine in the

central nervous system (MACMILLAN et al., 2008), which is also seen as an effect of clonidine, which is responsible for the reduction of sympathetic outflow (HYSEK et al., 2012; OGATA & DODMAN, 2011; MITCHELL et al., 2005). In this way, these complementary mechanisms of reducing neuronal epinephrine uptake by tramadol and clonidine may have resulted in the additive autonomic effect, due to the potentiation of the sympathetic block.

Table 1 - Comparison of total time of registration of the heart rate variability, and heart rate (minimum, mean and maximum), and arterial blood pressure (SAP, DAP, MAP) values (average ± standard deviation) between control (CG) and clonidine (CLG) groups.

Variables	CG	CLG	P*
MeanNN (ms)	584.5±62.77	680.5±75.01	0.0371
SDNN (ms)	97.83±28.94	163.8±49.81	0.0186
SDANN (ms)	63.83±21.55	102.3±32.89	0.0374
SDNNI (ms)	60.83±28.53	110.2±42.92	0.0410
rMSSD (ms)	75.83±38.91	158.0±81.20	0.0494
pNN>50 (%)	21.87±15.82	39.00±15.63	0.0886
HRmin (bpm)	65.83±6.853	52.50±9.524	0.0193
HRmean (bpm)	107.8±8.542	91.83±8.542	0.0088
HRmax (bpm)	212.5±29.68	188.3±29.68	0.2605

* Paired *t* test p value; MeanNN - average of all regular R-R (NN) intervals; SDNN - standard deviation (SD) of all regular NN intervals; SDANN - SD of 5-minutes average NN intervals; SDNNi - Mean of the SD of all NN intervals for all 5-minute segments; rMSSD - Square root of the mean of the squares of successive NN interval differences; pNN> 50 - Percentage of intervals longer than 50ms different from preceding interval; HRmin – minimal heart rate; HRmean – average heart rate; HRmax – maximum heart rate.

Eventhough this synergic effect has been observed only in one HRV variable (meanNN), the association of clonidine and tramadol should be avoid considering the risk to develop cardiac conduction disturbances as observed in this two dogs. This kind of conductance disturbance was also noticed in dogs anesthetized at different doses of clonidine, induced by etomidate and maintained in halothane anesthesia (DEROSSI et al., 2007). However, in the referred study clonidine was intravenously administrated and there is no

description about the moment of occurrence of the electric disturbance. Nonetheless, future investigations must be done to clarify the synergic mechanisms of tramadol and clonidine.

The values of MeanNN were also higher in the CLG at times T8 and T10 ($p<0.05$), although only in the T10 time the superiority of CLG was notice for SDNN and rMSSD variables ($p<0.05$), suggesting increase in parasympathetic tone and decrease in sympathetic tone at these moments, especially in T10 (table 2, figure 1). Considering the reduction on anesthetic drug rate and sedative effect at the extubation time (T10), is correct to assume that the autonomic balance, with an increase in heart sympathetic and decrease of parasympathetic influence, tend to occur in a proportional way of anesthetic recover, which were delayed in CLG compared to CG at this time (T10). No difference in time to the extubation procedure was observed ($p>0.05$) between the CG (139.2±18.96 minutes) and CLG (132.3±9.20 minutes), which probably had no influence on the groups observed differences.

The arterial blood pressure was also compared into groups every 10 minutes, during 60 minutes after tramadol administration. However, instead of the expected reduction on CLG none difference on SAP, DAP and MAP was observed, in any time (Table 3 and figure 2). The main effect of clonidine over blood pressure can be caused by multiple mechanisms like a stimulation of alfa-2 adrenoreceptors in the brains steam attenuating sympathetic and increasing the parasympathetic outflow (HYSEK et al., 2012; MITCHELL et al., 2005), resulting in hypotension. In an opposite way, the vascular activation of the alpha2-adrenoreceptors results in vasoconstriction and hypertensive effect (LEINO et al. 2020).

However, the spinal administration of clonidine in dogs reveals a biphasic behavior of arterial blood pressure, initiating with hypertensive status by a vasoconstriction alpha2-agonist action, followed by a secondary hypotension mediated by a baroreflex activity, increasing the heart parasympathetic outflow (LEINO et al., 2020).Eventhough the possibilities of differences effects related to a different rout of clonidine administration, we

not believe that biphasic phenomenal had been occurred at CLG dogs, considering none decrease was observed at HRV variables after clonidine administration, compared to CG, as expected in an initial vascular action of clonidine.

Table 2 – Time domain heart rate variability on different times of evaluation in a control (CG) and Clonidine (CLG) groups of dogs.

Times	Grupos	NNmédio	SDNN	rMSSD	pNN>50
T0	**CG**	513,70±75,83	102,20±34,64	123,00±67,69	45,64±15,91
	CLG	550,20±98,28	116,30±41,38	134,00±61,99	50,81±23,98
T1	**CG**	546,80±113,10	112,80±49,39	125,50±81,90	45,58±19,87
	CLG	649,00±125,40	157,00±62,89	203,50±127,50	58,44±30,97
T2	**CG**	513,50±78,35	97,17±39,18	67,17±24,28	16,97±3,69
	CLG	593,20±113,00	86,83±37,84	57,50±42,20	16,49±15,97
T3	**CG**	616,70±52,19	43,50±28,50	28,00±18,53	9,81±11,32
	CLG	680,20±56,14	75,00±30,65	56,83±44,21	20,58±23,41
T4	**CG**	643,70±123,10*****	51,83±64,37	64,50±92,59	23,63±35,86
	CLG	819,80±78,77	118,50±124,00	161,20±210,80	50,65±26,38
T5	**CG**	634,50±88,07	46,17±55,27	50,67±61,08	21,49±32,27
	CLG	780,50±71,96	68,17±57,46	79,83±85,56	34,17±33,30
T6	**CG**	640,20±74,98	44,00±38,08	52,33±58,95	21,80±33,49
	CLG	752,30±74,31	57,83±35,31	61,00±57,45	28,43±32,36
T7	**CG**	647,70±64,60	48,67±37,85	54,67±61,70	25,52±33,93
	CLG	762,30±34,85	73,67±44,71	79,50±59,14	33,94±29,72
T8	**CG**	599,20±35,66*****	39,67±25,71	35,17±27,01	15,58±19,37
	CLG	785,00±52,13	87,67±61,08	112,30±93,64	48,89±33,20
T9	**CG**	606,30±64,30	34,00±16,75	31,67±21,59	13,28±15,13
	CLG	750,70±90,37	90,33±64,17	104,80±101,30	41,44±37,96
T10	**CG**	598,70±84,75*****	49,83±33,49*****	43,50±33,86*****	16,51±17,81
	CLG	852,50±188,60	193,80±143,40	314,20±294,60	60,04±34,45

*Represent a statistical difference between groups (CG and CLG) in each time of evaluation, attested by Bonferroni test ($p<0,05$); MeanNN - average of all regular R-R (NN) intervals; SDNN - standard deviation (SD) of all regular NN intervals; rMSSD - Square root of the mean of the squares of successive NN interval differences; pNN> 50 - Percentage of intervals longer than 50ms different from preceding interval.

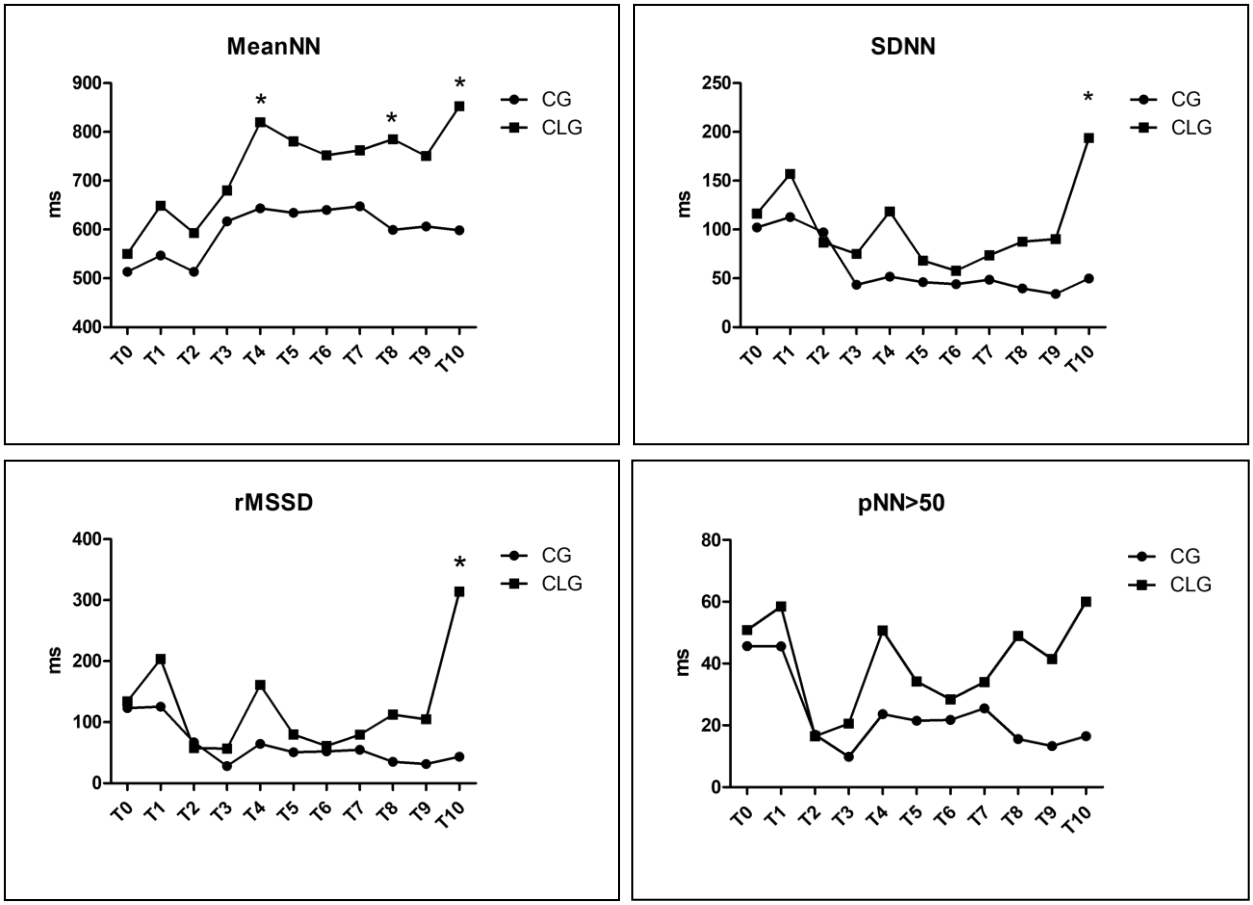

Figure 1 - Time domain heart rate variability on different times of evaluation in a control (CG) and Clonidine (CLG) groups of dogs. ***** Represent a statistical difference between groups (CG and CLG) in each time of evaluation, attested by Bonferroni test ($p<0,05$); MeanNN - average of all regular R-R (NN) intervals; SDNN - standard deviation (SD) of all regular NN intervals; rMSSD - Square root of the mean of the squares of successive NN interval differences; pNN> 50 - Percentage of intervals longer than 50ms different from preceding interval.

However, as a study limitation, the initial hypertensive phase was probably not registered by a necessity of the anesthesia induction to obtain an invasive method applied, to accompany the arterial blood pressure in the evaluated dogs. Future studies could elucidate this hypothesis of biphasic behavioral of arterial blood pressure in dogs receiving intramuscular clonidine, and its association with a baroreflex mechanism on HRV.

Table 3 – Average and standard deviation values of systolic (SAP), diastolic (DAP), and mean (MAP) arterial blood pressure, on different times of evaluation in a control (CG) and Clonidine (CLG) groups of dogs.

Times	Grupos	SAP	DAP	MAP
Zero	**CG**	78,50±12,34	58,12±11,80	66,12±11,89
	CLG	77,62±6,41	55,50±2,33	63,75±2,81
10	**CG**	82,50±7,96	57,00±8,88	69,37±7,19
	CLG	81,25±12,12	55,75±6,31	65,50±7,85
20	**CG**	85,00±6,02	59,75±6,06	71,37±3,66
	CLG	77,87±9,32	54,75±5,33	63,25±5,36
30	**CG**	84,50±4,14	62,62±7,04	75,25±6,40
	CLG	79,85±13,28	57,37±10,23	66,50±9,65
40	**CG**	87,50±3,20	60,87±4,18	72,25±2,12
	CLG	81,12±13,98	61,50±10,98	67,50±12,45
50	**CG**	89,37±5,70	63,50±4,24	74,87±4,94
	CLG	8050±13,44	62,62±8,55	69,50±8,83
60	**CG**	92,75±4,97	64,62±4,24	76,75±4,95
	CLG	86,00±10,21	62,25±6,62	71,12±7,14

Eventhough no differences on arterial pressure were observed into groups, at the different moments, the SAP, MAP, and MAP showed a tendency to increase along the evaluated times in both groups (figure 2). Beside the dual effect of clonidine on arterial blood pressure discussed before, other possibilities for this result involve the increase on vascular resistance and arterial pressure produced by tramadol (ITAMI et al., 2011).

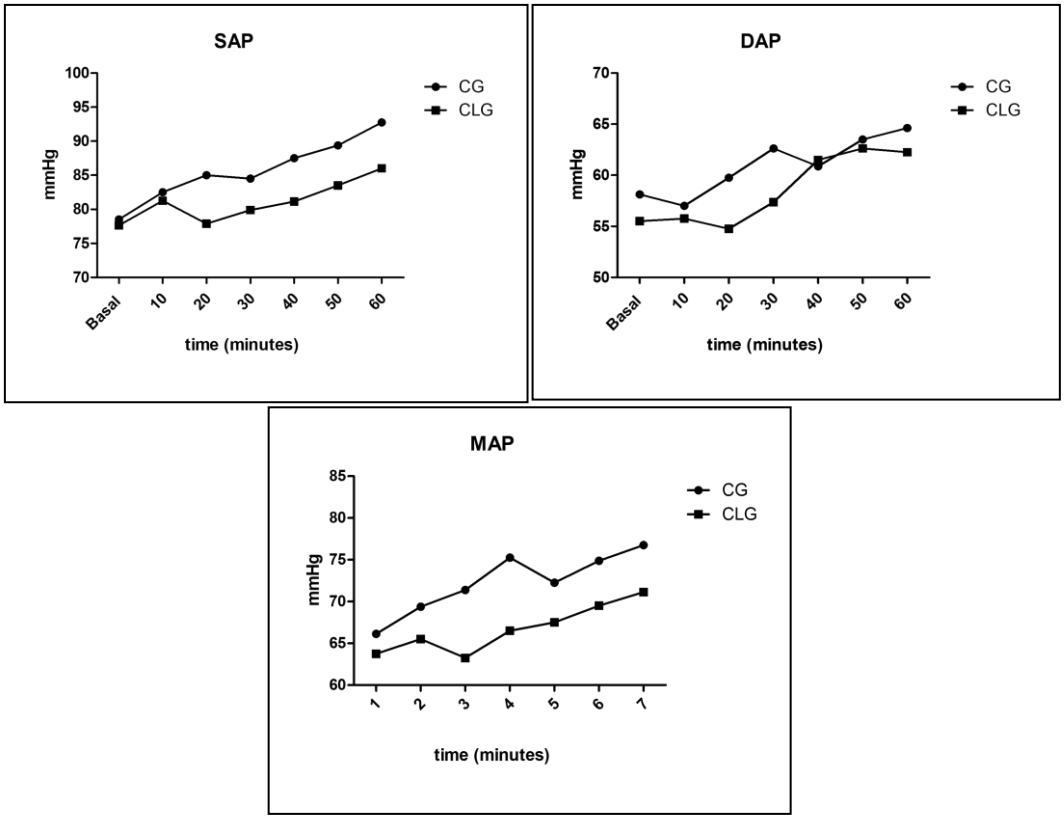

Figure 2 - Average values of systolic (SAP), diastolic (DAP), and mean (MAP) arterial blood pressure obtain along times of evaluation, in a control (CG) and Clonidine (CLG) groups of dogs.

Many physiological components can also influence the arterial pressure modulation of clonidine as a compensatory baroreflex mechanism (LEINO et al. 2020), modulation of postganglionic sympathetic cardiac nerves (MAZE & TRANQUILLI, 1991), and decrease in cardiac output. The ways of administration, dose, and the possible interactive effect with other drugs should be also considered (FERREIRA DA CRUZ, et al., 2011; LEINO et al. 2020), as observed in HRV in a tramadol time (T4). In the present study, a sample size can also be a limitation to evidence these expected statistical differences on arterial pressure values.

2.4.CONCLUSION

Thus, it is possible to conclude that the intramuscular dose of 5µg.kg-1 of clonidine, as pre-anesthetic medication in healthy dogs, associated with tramadol (analgesia), propofol

(induction of anesthesia), and isoflurane (maintenance) increases the time domain HRV by sympathetic outflow block and increment on parasympathetic tonus, without important expressions on arterial blood pressure, which was associated to the occurrence of second-degree atrioventricular block (Mobitz II), accentuated by the autonomic synergic effect of tramadol.

Although the pre-anesthetic use of clonidine in dogs with fear-based behavioral problems should be considered, its association with tramadol is discouraged due to the cardiovascular risk evidenced.

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3. CONCLUSÃO

Desta forma é possível concluir que a dose intramuscular de 5µg.kg-1 de clonidina, como medicação pré-anestésica, compondo um protocolo anestésico incluindo tramadol (analgesia), propofol (indução da anestesia) e isoflurano (manutenção) em cães saudáveis, resulta em aumento no domínio do tempo VFC sem alteração da pressão arterial (PAS, PAD e PAM). Esses resultados sugerem o incremento da influência parassimpática do coração e a supressão do fluxo simpático pelo uso da clonidina, principalmente após a combinação do tramadol, e no momento da extubação.

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