UNIVERSIDADE FEDERAL DA FRONTEIRA SUL
***CAMPUS* REALEZA**
PROGRAMA DE PÓS GRADUAÇÃO EM SAÚDE, BEM-ESTAR E PRODUÇÃO ANIMAL SUSTENTÁVEL NA FRONTEIRA SUL

MARINA MARANGONI

EFEITOS CARDIOVASCULARES E COMPORTAMENTAIS DA DEXMEDETOMIDINA ISOLADA OU ASSOCIADA À GABAPENTINA EM GATOS SAUDÁVEIS

REALEZA
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Dissertação de mestrado apresentada para Programa de Pós-Graduação em Saúde, Bem-Estar e Produção Animal Sustentável, da Universidade Federal da Fronteira Sul (UFFS) – *Campus* Realeza, como requisito parcial para obtenção do título de mestre.

Orientadora: Profª. Drª. Tatiana Champion

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REALEZA

2025

Bibliotecas da Universidade Federal da Fronteira Sul - UFFS

Marangoni, Marina
EFEITOS CARDIOVASCULARES E COMPORTAMENTAIS DA DEXMEDETOMIDINA ISOLADA OU ASSOCIADA À GABAPENTINA EM GATOS SAUDÁVEIS / Marina Marangoni. -- 2025.
69 f.:il.

Orientadora: Drª Tatiana Champion
Co-orientadora: Drª Gabrielle Coelho Freitas
Dissertação (Mestrado) - Universidade Federal da Fronteira Sul, Programa de Pós-Graduação em Saúde, Bem-Estar e Produção Animal Sustentável Na Fronteira Sul, Realeza,PR, 2025.

1. gabapentina. 2. felinos. 3. estresse. I. , Tatiana Champion, orient. II. Freitas, Gabrielle Coelho, co-orient. III. Universidade Federal da Fronteira Sul. IV. Título.

Elaborada pelo sistema de Geração Automática de Ficha de Identificação da Obra pela UFFS com os dados fornecidos pelo(a) autor(a).

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Este trabalho foi defendido e aprovado pela banca em 19/03/2025

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AGRADECIMENTOS

À minha amada **Ana**, minha parceira de vida. Tu és uma forma de ser eu, e eu uma forma de te ser. Viver contigo é o elixir para qualquer adversidade. Agradeço a Deus por ter entrelaçado nossos caminhos, em ti vejo um amor que se revela nas pequenas coisas que, de tão simples, se tornam grandes. Obrigada por me amar e por estar ao meu lado, esse trabalho só foi possível com o teu apoio. Cada segundo da pesquisa, senti tua presença e cuidado, e meu amor por ti se reflete em cada letra desta dissertação.

Aos meus pais, **Edriane e Flávio**, agradeço por serem os pilares que me sustentam. Sinto que só eu, nesse vasto mundo, tive a sorte de ser filha de vocês. O amor de vocês é imensurável e imensurável também seria a capacidade de serem pais de milhares, mas ainda assim, seria pouco. Vocês me deram as asas para voar e continuam a me apoiar em cada jornada, longe ou perto. Em qualquer lugar, vocês serão meu lar.

À **Mada e Pado**, meus segundos pais. Obrigada por me adotarem como filha, me cobrindo com tanto amor, que sei que posso sempre me aquecer nele. Agradeço também por cuidarem de mim de longe, sempre fazendo o possível para estar perto.

À minha orientadora, **Profª Drª Tatiana Champion**, agradeço profundamente por ter me acolhido e acreditado no meu potencial na cardiologia. Sou imensamente grata por todo o empenho na pesquisa e pelas oportunidades que você me ofereceu durante o mestrado. É um privilégio contar com uma orientadora que dedica tanto tempo e carinho como você, sempre com a preocupação de buscar o melhor para nossos pacientes.

À minha coorientadora, **Profª Drª Gabrielle Coelho Freitas**, agradeço pelos sete anos de trajetória sob sua orientação. Agradeço por me escolher, mesmo quando eu ainda nem sabia o que era anestesiologia, e por ter sido a responsável pela minha paixão por essa área. Toda minha paixão se deve a você. Agradeço pelo apoio, e mesmo distante, sempre sinto sua proximidade.

Ao **Profº Drº Paulo Henrique Braz**, que me acolheu e adotou no S.A.A.S. Agradeço pelas inúmeras oportunidades, pelas experiências, pela parceria e pela amizade. Admiro profundamente quem você é como professor, veterinário e ser humano. Você é uma inspiração em todas as áreas.

A todos os **colegas de pesquisa**, minha eterna gratidão. Sinto-me feliz em afirmar que todos vocês são mais do que colegas, são amigos: Ana Marques, Ademar Fagundes, Ana Castanho, Gabryel Leonardo, Valéria Silvestri, Pamela Busato, Vitor Mamgue, Emanuel Caon e Mel Takazono.

À **Dodô** (in memoriam) e **Caju** (in memoriam), nossas amadas gatinhas. Vocês foram muito mais que animais de estimação, foram parte do nosso coração. Já eram anjos enquanto aqui estavam, e o amor por vocês segue vivo, com saudades. À **Sol** (in memoriam) e **Alvin** (in memoriam), nossos irmãos caninos. Lembrar de vocês, com seu cheirinho de sono e latido alegre, será sempre uma doce lembrança que guardarei com carinho.

Agradecimento especial aos **tutores dos gatos e aos 52 gatos** que fizeram parte deste projeto: Saray, Zelda, Evee, Fumaça, Keisse, Thomas, Frajola, Fanta, Oliver, Frodo, Draco, Catarina, Concreto, Megume, Cristina, Rita, Batgirl, Mimi, Murilo, Estrelinha, Tequila, Corote, Katniss, Jaci, Erê, Pétala, Douglas, Amora, Luiz Inácio, Raul, Raquel, Romeu, Neni, Rico, Mime, Maninha, Gata, Tina, Ísis, Laranjinha, Lua, Madá, Rafael, Pandora, Mel, Mingau, Branca, Princesa, Nairóbi, Amora, Nenê, Floquinho.

Ouça, Virgínia, é preciso amar o inútil. Criar pombos sem pensar em comê-los, plantar roseiras sem pensar em colher as rosas, escrever sem pensar em publicar, fazer coisas assim, sem esperar nada em troca. A distância mais curta entre dois pontos pode ser a linha reta, mas é nos caminhos curvos que se encontram as melhores coisas (Lygia Fagundes Telles, Ciranda de Pedra)

RESUMO

O estresse em gatos é um fator crítico em ambientes clínicos, pois pode comprometer a acurácia diagnóstica. Assim, protocolos anestésicos que otimizem doses e equilibrem efeitos são essenciais para minimizar complicações. A dexmedetomidina é amplamente utilizada na sedação felina, mas pode causar bradicardia e alterações pressóricas. A gabapentina é empregada como ansiolítico, auxiliando no manejo clínico sem impacto hemodinâmicos significativos. Este estudo avaliou os efeitos sedativos e cardiovasculares dessa associação em gatas. O estudo envolveu 52 gatas divididas em dois grupos, que receberam gabapentina (100 mg/gato via oral) ou placebo. Após 90 minutos, foram avaliados parâmetros fisiológicos, escores de sedação e estresse e ecocardiografia. Os pontos de avaliação foram compostos por M0 (avaliação basal pré-medicação), M1 (avaliação 90 minutos após a administração de gabapentina/placebo) e M2 (avaliação 30 minutos após a administração de dexmedetomidina). Em seguida, os grupos foram subdivididos para receber dexmedetomidina em dose baixa ou alta. A análise dos dados foi realizada por meio de ANOVA para dados paramétricos, seguida dos testes post hoc de Holm. O nível de significância foi estabelecido em $p < 0,05$. Os resultados demonstraram que a gabapentina não potencializou a sedação induzida pela dexmedetomidina nem reduziu o estresse, conforme indicado pelos escores semelhantes de CSS e FMSS entre os grupos. Entretanto, a associação da gabapentina com dose elevada de dexmedetomidina resultou em maior incidência de regurgitação valvar, predominantemente mitral e tricúspide, além de redução mais acentuada da frequência cardíaca. A ecocardiografia revelou aumento significativo no tempo de ejeção e redução do débito cardíaco em alguns grupos, embora sem diferenças globais entre os protocolos. Esses achados sugerem que a gabapentina pode influenciar parâmetros cardiovasculares sem intensificar a sedação, ressaltando a necessidade de investigações adicionais para elucidar os mecanismos envolvidos e sua relevância clínica na anestesia veterinária.

Palavras-chave: felinos, sedativos, interação medicamentosa, ansiolítico, tranquilização.

ABSTRACT

Stress in cats is a critical factor in clinical settings, as it can compromise diagnostic accuracy. Therefore, anesthetic protocols that optimize drug doses while balancing their effects are essential to minimize complications. Dexmedetomidine is widely used for feline sedation but may cause bradycardia and blood pressure alterations. Gabapentin is employed as an anxiolytic, aiding in clinical management without significant hemodynamic impact. This study evaluated the sedative and cardiovascular effects of this drug combination in female cats. A total of 52 cats were divided into two groups, receiving either gabapentin (100 mg/cat orally) or a placebo. After 90 minutes, physiological parameters, sedation and stress scores, and echocardiographic assessments were recorded. Evaluation time points included M0 (baseline premedication assessment), M1 (90 minutes post-gabapentin/placebo administration), and M2 (30 minutes post-dexmedetomidine administration). Subsequently, the groups were subdivided to receive either a low or high dose of dexmedetomidine. Data analysis was performed using ANOVA for parametric data, followed by Holm post hoc tests. Significance was set at $p < 0.05$. The results demonstrated that gabapentin did not enhance dexmedetomidine-induced sedation or reduce stress, as indicated by similar CSS and FMSS scores across groups. However, the combination of gabapentin with a high dose of dexmedetomidine resulted in a higher incidence of valvular regurgitation, predominantly mitral and tricuspid, along with a greater reduction in heart rate. Echocardiographic evaluation revealed a significant increase in ejection time and a decrease in cardiac output in some groups, although no overall differences were observed between protocols. These findings suggest that gabapentin may influence cardiovascular parameters without enhancing sedation, highlighting the need for further investigations to elucidate the underlying mechanisms and their clinical relevance in veterinary anesthesia.

Keywords: feline, sedation, drug interaction, anxiolytic, tranquilization.

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1 INTRODUÇÃO

O estresse em felinos é um fator crítico em ambientes clínicos, pois pode comprometer significativamente o comportamento, os parâmetros fisiológicos e a acurácia diagnóstica, interferindo em exames e procedimentos clínicos e cirúrgicos. Devido ao temperamento ansioso e defensivo, gatos frequentemente necessitam de doses elevadas de tranquilizantes ou sedativos, o que pode resultar em depressão respiratória e cardiovascular (GRUBB *et al*., 2020). Dessa forma, a elaboração de protocolos anestésicos que otimizem a dose de fármacos e equilibrem seus efeitos é essencial para minimizar complicações anestésicas.

A gabapentina, um ansiolítico amplamente utilizado na medicina veterinária, é frequentemente administrada em gatos antes do transporte ou de visitas veterinárias para reduzir o estresse e facilitar o manejo (VAN HAAFTEN *et al.*, 2017). Sua administração pelo menos 90 minutos antes do manejo está alinhada com sua concentração plasmática máxima, o que garante atingir seus efeitos terapêuticos (SIAO; PYPENDOP; ILKIW, 2010). Apesar do seu uso disseminado para redução do estresse antes de procedimentos, mais estudos são necessários para avaliar sua eficácia como pré-medicação em animais submetidos à sedação e anestesia.

A gabapentina age ligando-se à subunidade α2δ dos canais de cálcio voltagem dependentes, inibindo a liberação de neurotransmissores excitatórios e promovendo efeitos ansiolíticos e analgésicos. Por não apresentar efeitos hemodinâmicos significativos, torna-se uma opção interessante quando se busca controle da ansiedade e dor sem comprometer a estabilidade cardiovascular (CALANDRE; VILLADEMOROS; SLIM, 2016). Além disso, ao reduzir a fusão das ondas de preenchimento do ventrículo esquerdo, a gabapentina melhora a função diastólica nas avaliações ecocardiográficas, o que reforça seu potencial como adjuvante anestésico (VERONEZI *et al.,* 2022). No entanto, seu impacto clínico, particularmente em combinação com a outros fármacos, não deve ser negligenciado.

Entre os agentes sedativos utilizados em felinos, a dexmedetomidina, um agonista altamente seletivo dos receptores α-2 adrenérgicos, tem se mostrado eficaz na promoção de sedação e analgesia, além de reduzir a necessidade de outros agentes anestésicos (SMITH *et al.,* 2017). Seus efeitos são dose-dependentes e podem ser obtidos isoladamente ou em combinação com outros medicamentos, dentro de uma faixa de doses de 2 a 20 μg/kg para induzir sedação. A concentração plasmática máxima da gabapentina, após administração

intramuscular, é observada 30 minutos após a administração e permanece estável até aproximadamente 100 minutos (PYPENDOP; HONKAVAARA; ILKIW, 2017).

Estudos indicam que a dexmedetomidina pode causar alterações hemodinâmicas, como aumento da resistência vascular e diminuição da frequência cardíaca, efeitos dependentes da dose (MUÑOZ *et al.*, 2017). Sua atuação nos receptores α2 pré-sinápticos reduz a liberação de norepinefrina, podendo ocasionar efeitos adversos, como vasoconstrição (PANZER; MOITRA; SLADEN, 2009). Além disso, em altas doses, a dexmedetomidina pode desencadear alterações pressóricas bifásicas, com aumento inicial da pressão arterial, seguido por uma redução progressiva e aumento reflexo da frequência cardíaca (LIU; KANG; WANG, 2021).

Além disso, há evidências de que a dexmedetomidina pode exercer efeito cardioprotetor ao reduzir a liberação de catecolaminas e modular a resposta simpática, minimizando danos oxidativos e apoptose no músculo cardíaco durante eventos isquêmicos (TAKAHASHI *et al.*, 2023). Contudo, seu uso também está associado a alterações cardiovasculares relevantes, incluindo redução do débito cardíaco e aumento da resistência vascular sistêmica e das pressões venosa central e pulmonar (RANKIN, 2017).

A dexmedetomidina é amplamente utilizada na sedação em gatos, no entanto seus efeitos cardiovasculares podem influenciar as variáveis ecocardiográficas (SLINGSBY; MURREL; TAYLOR, 2010; SANTOS; LUDDERS; ERB, 2010). A ecocardiografia é essencial para o rastreamento de doenças cardíacas, como a cardiomiopatia hipertrofia (HCM), a cardiomiopatia mais comum em gatos (HAGGSTROM; LUIS; WESS, 2015). Embora muitos gatos tolerem o exame sem necessidade de sedação, alguns indivíduos requerem sedação para viabilizá-lo (HAGGSTROM; ANDERSSON; FALK, 2016). No entanto, agentes sedativos podem alterar os parâmetros cardiovasculares, afetando potencialmente a precisão diagnóstica (SINCLAIR *et al*., 2003).

Os efeitos cardiovasculares dos agonistas α2-adrenérgicos já foram investigados em cães e gatos (WANG *et al.*, 2016), mas os dados sobre a combinação de dexmedetomidina e gabapentina ainda são limitados. Existe apenas um estudo que avaliou a combinação de gabapentina e dexmedetomidina, demonstrando seu potencial para melhorar a sedação e a analgesia (RUTHERFORD *et al.*, 2021). Este estudo tem como objetivo avaliar os efeitos da dexmedetomidina e da gabapentina sobre a sedação, o estresse, os parâmetros fisiológicos e ecocardiográficos em gatos saudáveis, com o objetivo de otimizar os protocolos anestésicos e melhorar o controle do estresse e das variáveis fisiológicas durante os procedimentos clínicos.

2 REVISÃO DE LITERATURA

2.1 MECANISMOS FISIOLÓGICOS DO ESTRESSE

O estresse é uma resposta fisiológica adaptativa a estímulos adversos, resultando na ruptura da homeostase. Esse processo ocorre em três fases: alerta, caracterizada pela ativação do eixo simpático-adrenal e do eixo hipotálamo-hipófise-adrenal (HHA); resistência, na qual o organismo busca se adaptar ao agente estressor; e exaustão, fase associada à incapacidade de manutenção da resposta adaptativa, podendo levar ao estresse crônico (SELYE, 1956).

A resposta ao estresse pode ser influenciada por fatores ambientais, fisiológicos e sociais, desencadeando alterações neuroendócrinas e comportamentais (PEREIRA; FARO; PEREIRA, 2013). Em animais, agentes estressores incluem mudanças climáticas, interações sociais e variações nutricionais, podendo comprometer o bem-estar (HAFEZ, 1968).

A ativação do sistema nervoso simpático promove a liberação de catecolaminas, como epinefrina e norepinefrina, resultando na resposta de "luta ou fuga". Esse mecanismo envolve aumento da frequência cardíaca, vasodilatação muscular, elevação da glicose sanguínea e inibição de funções fisiológicas não essenciais (MICHAEL *et al.*, 2007). Paralelamente, a ativação do eixo HHA leva à liberação de glicocorticoides, como cortisol e corticosterona, regulando o metabolismo energético, o sistema imunológico e a resposta inflamatória (HERMAN *et al*., 2011).

A intensidade e a duração da resposta ao estresse variam conforme o tipo de agente estressor, o estado fisiológico e a capacidade adaptativa do organismo (GOLDSTEIN; KOPIN, 2007). Quando persistente, o estresse crônico pode gerar impactos negativos, incluindo imunossupressão, distúrbios metabólicos e alterações comportamentais (ROMERO, 2004).

2.2 INFLUÊNCIA DO ESTRESSE NOS PARÂMETROS FISIOLÓGICOS

2.2.1 Pressão arterial

A pressão arterial é um parâmetro influenciado por alterações autonômicas decorrentes de estresse, medo ou excitação, fatores que podem comprometer a acurácia das medições em ambiente clínico. A elevação transitória da pressão arterial em resposta a essas condições é

denominada hipertensão situacional, caracterizada por um aumento temporário dos valores pressóricos sem implicações patológicas, mas que pode levar a interpretações diagnósticas equivocadas (CUSPIDI *et al.*, 2016)

Para minimizar interferências associadas à ansiedade, recomenda-se a adoção de técnicas que garantam conforto ao animal durante o procedimento. A maioria dos pacientes tolera melhor a aferição em decúbito esternal ou posição sentada, e as medições devem ser repetidas pelo menos cinco vezes para obtenção de uma média confiável (CABRAL *et al.*, 2010).

2.2.2 Temperatura, frequência cardíaca e frequência respiratória

O estresse influencia diretamente parâmetros fisiológicos como as frequências cardíaca e respiratória, sendo essas alterações mediadas pela liberação de catecolaminas, especialmente a adrenalina. Esse mecanismo prepara o organismo para uma resposta de fuga ou luta, resultando em taquicardia, aumento da frequência respiratória, elevação da pressão arterial e mobilização de substratos energéticos, enquanto funções não essenciais, como digestão e reprodução, são temporariamente suprimidas (BOWEN; HEATH, 2005).

Estudos demonstram que o ambiente influencia diretamente essas respostas. Em gatos, observou-se aumento significativo da frequência cardíaca, da frequência respiratória e da pressão arterial em ambiente hospitalar, quando comparado a medições domiciliares, evidenciando o impacto do ambiente na modulação autonômica desses parâmetros (QUIMBY; SMITH; LUNN, 2011).

A temperatura corporal também pode ser alterada pelo estresse por meio da ativação do sistema nervoso autônomo. Em roedores, níveis elevados de noradrenalina no locus coeruleus estimulam a produção de prostaglandinas na área pré-óptica do hipotálamo, afetando a termorregulação e resultando em hipertermia induzida pelo estresse (OKA; HORI, 2001).

2.3 O ESTRESSE EM GATOS

O estresse em gatos pode ser desencadeado por diversos fatores ambientais e sociais, incluindo mudanças na rotina, sons e odores desconhecidos. A visita a um ambiente clínico veterinário, por exemplo, representa uma situação potencialmente estressante, pois envolve

exposição a novos estímulos sensoriais, separação do tutor e contenção física (DYBDALL; STRASSER; KATZ, 2007).

O medo e a ansiedade são respostas adaptativas ao estresse, desempenhando um papel fundamental na sobrevivência da espécie. No entanto, quando intensas ou prolongadas, essas respostas podem comprometer o bem-estar do animal e dificultar sua manipulação (BOWEN; HEATH, 2005). Além dos fatores emocionais, condições médicas também podem impactar o comportamento felino, desencadeando comportamentos agressivos. Dessa forma, a avaliação clínica detalhada é essencial para diferenciar estresse e dor como causas do comportamento alterado (OVERALL *et al.*, 2005).

As manifestações fisiológicas do estresse incluem aumento das frequências cardíaca e respiratória, pressão arterial e alterações comportamentais e metabólicas (GREGORY, 2004). Estudos indicam que experiências precoces, como as primeiras consultas veterinárias, podem influenciar o comportamento do gato na vida adulta, tornando-o mais resistente ou mais suscetível ao estresse em situações similares (GODBOUT; FRANK, 2011).

A relutância dos tutores em levar seus gatos ao veterinário é amplamente associada ao estresse manifestado pelos animais durante o transporte e o atendimento (AVMA, 2018). Como consequência, muitos felinos recebem cuidados médicos menos frequentes do que cães, aumentando o risco de doenças não diagnosticadas e impacto negativo na saúde geral da espécie (HOYUMPA *et al*., 2010).

Estudos têm sido conduzidos para desenvolver estratégias que minimizem o estresse em ambiente clínico, facilitando o manejo e melhorando a experiência tanto para o paciente quanto para o veterinário (KESSLER; TURNER, 1997; QUIMBY; SMITH; LUNN, 2011; RODAN *et al*., 2011).

2.4 MEDIDAS FARMACOLÓGICAS PARA CONTROLE DO ESTRESSE EM GATOS

A identificação precoce de sinais de estresse em gatos é fundamental para prevenir reações adversas durante o manejo clínico. Alguns pacientes podem demandar a contenção química, especialmente em situações que apresentam risco à segurança da equipe ou quando a duração do procedimento pode intensificar o estresse do paciente. O uso de fármacos ansiolíticos e sedativos tem sido estudado como estratégia para minimizar o desconforto desses animais e facilitar sua manipulação. Entre as opções farmacológicas, a gabapentina e a

dexmedetomidina são amplamente estudadas e utilizadas para controle do estresse em gatos (SMITH *et al*., 2020; VAN HAAFTEN *et al*., 2017).

A gabapentina, quando administrada via oral, demonstrou ser eficaz na redução da ansiedade e na promoção da sedação leve, o que facilita a manipulação do animal em ambientes veterinários. Seu efeito ansiolítico é particularmente útil em situações de estresse causado pela visita ao veterinário, ajudando a reduzir o medo e a agressividade, sem causar sedação excessiva, o que permite que o gato se mantenha mais colaborativo durante os procedimentos (VAN HAAFTEN *et al*., 2017).

Por outro lado, a dexmedetomidina tem se mostrado eficiente na sedação e no controle do estresse em gatos. Como agonista dos receptores α-2 adrenérgicos, promove sedação profunda e efeito ansiolítico, o que facilita a manipulação do paciente e reduz significativamente a resposta de estresse. Além disso, sua administração apresenta a vantagem ser reversível por meio de antagonistas específicos, permitindo o controle preciso da sedação quando necessário (SANTOS *et al*., 2010).

Ambos os medicamentos têm se mostrado alternativas eficazes para a redução do estresse em gatos durante o atendimento veterinário, contribuindo para um manejo mais seguro e confortável para os animais, ao mesmo tempo que minimizam o impacto negativo do estresse sobre o bem-estar deles. A escolha entre gabapentina e dexmedetomidina depende do tipo de procedimento, da resposta do animal e dos objetivos terapêuticos específicos.

2.5 USO DA GABAPENTINA EM GATOS

A gabapentina é um medicamento amplamente utilizado em gatos para controle de ansiedade, proporcionando efeitos tranquilizantes sem os efeitos colaterais indesejáveis frequentemente associados a outras drogas sedativas (HUDEC; GRIFFIN, 2020). A gabapentina, um análogo estrutural do ácido γ-aminobutírico (GABA), é amplamente utilizada como adjuvante anticonvulsivante e analgésico, especialmente em humanos, para o tratamento da dor neuropática (MOORE *et al*., 2011).

Ao contrário do seu análogo GABA, a gabapentina não atua em receptores gabaérgicos, não interferindo na absorção ou metabolismo do GABA (CALANDRE; VILLADEMOROS; SLIM, 2016). Este medicamento se liga à subunidade acessória alfa2delta (α2δ) dos canais de cálcio voltagem dependentes, localizados principalmente no

prosencéfalo e no corno espinhal dorsal, diminuindo a entrada de cálcio e proporcionando efeito inibitório que resulta no seu efeito ansiolítico (SIAO; PYPENDOP; ILKIW, 2010).

A gabapentina foi originalmente sintetizada como um fármaco destinado ao controle da espasticidade, entretanto se mostrou eficiente como anticonvulsivante e no controle da dor crônica e neuropática. Sua principal utilização na medicina veterinária é para controle de ansiedade em gatos, sendo usualmente administrada pela via oral previamente a consultas veterinárias, a fim de proporcionar maior bem-estar para os animais e possibilitar a realização de exames com redução do estresse causado pela manipulação (RODAN *et al*., 2011).

A ação da gabapentina na redução do estresse e ansiedade tem sido particularmente útil no contexto de situações estressantes, como o transporte para consultas veterinárias. Em um estudo recente, a administração de gabapentina reduziu a ansiedade dos gatos e facilitou a colocação na caixa de transporte, além de melhorar a experiência dos tutores (HUDEC; GRIFFIN, 2020). No entanto, os efeitos variam entre os indivíduos, com algumas respostas comportamentais mais pronunciadas do que outras (KRUSZKA *et al.*, 2021).

Medicamentos administrados pela via oral, como a gabapentina, têm sido amplamente utilizados para tranquilização em gatos, com intuito de promover efeitos ansiolíticos que facilitem o manuseio em ambiente hospitalar. Essa técnica possui maior facilidade de administração em comparação a medicações de administração intravenosa (IV), intramuscular (IM) ou subcutânea (SC) e pode ser utilizada como uma técnica prévia que auxilia na posterior aplicação de medicamentos por vias mais invasivas (ERICKSON *et al*., 2021).

Van Haaften *et al.* (2017), avaliaram os efeitos de dose única de gabapentina (100 mg/gato) no estresse durante avaliação veterinária e evidenciaram que gatos que receberam gabapentina apresentaram menores escores de estresse comparado a gatos que receberam tratamento placebo. Adicionalmente, outro estudo realizado em gatos com a mesma dosagem de gabapentina apresentou resultados positivos na tranquilização, sem alterações significativas nas variáveis fisiológicas e ecocardiográficas (VERONEZI *et al.,* 2022)

Estudos realizados por Hudec e Griffin (2021) demonstraram menores níveis de estresse, associados à manutenção dos níveis de cortisol e glicose, sem presença de sedação. Adicionalmente, Arguelles *et al.* (2021) observaram que a diminuição do estresse pré-operatório é eficaz em diminuir o período de latência dos fármacos administrados na medicação pré-anestésica, além de diminuir o requerimento anestésico de propofol no momento da indução anestésica de gatos. Portanto, medicamentos como a gabapentina, que reduzem os níveis de estresse, podem ser administrados para auxiliar no manejo anestésico (GRUBB *et al*., 2020).

Visando avaliar a influência da pré-medicação com gabapentina no requerimento de isoflurano, Johnson *et al.* (2019) administraram gabapentina (20 mg/animal) em cães submetidos a anestesia geral e, após sete dias, os mesmos animais foram submetidos a anestesia geral sem administração prévia de gabapentina. Os cães apresentaram menor requerimento de anestésico inalatório quando tratados com gabapentina, sem demonstrar alterações significativas nos parâmetros fisiológicos e hemodinâmicos.

Em gatos domésticos, a administração oral de gabapentina é bem absorvida, com uma biodisponibilidade de até 95% quando administrada em doses de 10 mg/kg (ADRIAN *et al.*, 2018). A dose recomendada para reduzir o estresse durante o transporte e consulta veterinária varia entre 50 e 150 mg por animal, administrada de 2 a 3 horas antes da visita ao veterinário (ROBERTSON *et al*., 2018; STEAGALL; SIMON, 2020). Estudos indicam que essa administração resulta em uma redução significativa nos escores de estresse e um aumento na sedação, facilitando a manipulação dos gatos durante os procedimentos (PANKRATZ *et al*., 2018; VAN HAAFTEN *et al.*, 2017).

A farmacocinética da gabapentina em gatos mostra que a droga tem uma meia-vida de eliminação de cerca de 3,5 horas, o que sugere uma absorção e eliminação eficientes. Doses de 10 mg/kg, administradas duas vezes ao dia, têm mostrado resultados variáveis em termos de eficácia analgésica, sugerindo que a dosagem ideal deve ser ajustada conforme as necessidades individuais de cada animal (ADRIAN *et al.*, 2018).

Em relação aos efeitos adversos, a gabapentina é geralmente bem tolerada, mas pode causar sonolência, ataxia, prolapso da terceira pálpebra e, em casos mais raros, vômito. A literatura também menciona o aumento da salivação excessiva, sedação exacerbada e redução significativa da frequência respiratória como possíveis efeitos colaterais (KRUSZKA *et al*., 2021; VAN HAAFTEN *et al*., 2017).

Em estudo realizado por Allen e LeBlanc (2019), foi avaliada a resposta hemodinâmica e ecocardiográfica de gatos saudáveis após administração de dose única de gabapentina. Os resultados mostraram ausência de diferenças significativas em frequência cardíaca, frequência respiratória ou pressão arterial sistólica, quando comparados ao momento inicial. No entanto, foi observada uma leve redução em parâmetros da função sistólica, como a fração de encurtamento, além de aumento no diâmetro ventricular e no volume atrial esquerdo.

Em termos de interações medicamentosas, a gabapentina pode ter sua absorção afetada por antiácidos, reduzindo sua eficácia (PAPICH, 2009). Além disso, os efeitos colaterais

podem ser potencializados quando administrada em conjunto com outros medicamentos que afetam o sistema nervoso central (QUINTERO, 2017).

2.6 USO DA DEXMEDETOMIDINA EM GATOS

Fármacos agonistas dos receptores α-2 adrenérgicos possuem propriedades farmacológicas variáveis, sendo comumente utilizados como adjuvantes anestésicos. Esses medicamentos atuam em receptores α-2 adrenérgicos, que têm como função mediar ações inibitórias pré e pós-sinápticas da noradrenalina no sistema nervoso central (SNC) e no sistema nervoso periférico (SNP) (MURREL, 2017). Eles são classificados nos subtipos α2A, α2B, α2C e α2D, tendo efeitos distintos. O subtipo α2A promove efeitos de analgesia, anestesia e sedação, enquanto o subtipo α2B está relacionado com a ocorrência de alterações cardiovasculares. O subtipo α2C é responsável por efeitos ansiolíticos e o subtipo α2D não apresenta efeitos específicos (RANKIN, 2017).

A dexmedetomidina é um medicamento agonista dos receptores α-2 adrenérgicos, altamente seletivo para esses receptores, que promove efeitos sedativos e analgésicos. Quando utilizada como medicação pré-anestésica, pode potencializar a ação de outros agentes e reduzir o requerimento de medicamentos de indução e agentes opioides e inalatórios trans-anestésicos (GREWAL, 2011; SMITH *et al*., 2017). Em felinos, a dexmedetomidina é frequentemente utilizada como medicação pré-anestésica ou adjuvante em protocolos anestésicos (ERICKSON *et al*., 2021; PAN *et al*., 2021).

Seus efeitos são dose-dependentes e pode ser utilizada isoladamente ou associada, em um intervalo de doses de 2 a 10 μg /kg, para promover sedação. Em doses superiores, há relatos de acentuação das alterações cardiovasculares, como aumento da resistência vascular sistêmica, pressão arterial e diminuição da frequência cardíaca (MUÑOZ *et al*., 2017). Sua ação ocorre principalmente nos receptores α2-adrenérgicos pré-sinápticos, sendo de 16 a 20 vezes mais potente do que nos receptores α1. A ativação desses receptores resulta na inibição da liberação de noradrenalina e na hiperpolarização neuronal, o que promove seu efeito sedativo (COURSIN; MACCIOLI, 2001; VITAL; ACCO, 2011).

A administração da dexmedetomidina deve ser realizada com cautela e em doses controladas, devido seus efeitos hemodinâmicos. Por ocasionar ativação de receptores α2 pré-sinápticos, este medicamento atenua a liberação de noradrenalina e consequentemente reduz a hipertensão por aumento da atividade simpática. Entretanto, quando administrada em altas

doses, produz efeito transitório de vasoconstrição mediada pela ativação dos receptores α2B (PANZER; MOITRA; SLADEN, 2009).

As alterações pressóricas observadas geralmente são bifásicas, sendo que a pressão arterial média (PAM) aumenta nos primeiros minutos e posteriormente diminui de 10 a 20% dos valores basais. Já a frequência cardíaca (FC) diminui significativamente nos primeiros minutos e então demonstra um aumento, porém ainda abaixo dos valores basais (LIU; KANG; WANG, 2021).

Estudos demonstraram que apesar dos seus efeitos sobre a PAM e FC, a dexmedetomidina pode exercer efeito cardioprotetor direto contra lesão de isquemia, por reduzir a liberação de catecolaminas e modular a resposta simpática. Além disso, pode atenuar a resposta inflamatória, o que minimiza danos oxidativos e de apoptose no músculo cardíaco durante períodos de isquemia, podendo apresentar efeitos protetores perante situações de hipóxia miocárdica (TAKAHASHI *et al*., 2023).

Entretanto, apesar dos estudos que demonstram seus efeitos cardioprotetores, há evidências de que sua administração ocasiona diversas alterações no sistema cardiovascular, incluindo severa redução da frequência cardíaca, do débito cardíaco (DC) e da oferta de oxigênio, bem como a elevação da resistência vascular sistêmica, pressão venosa central e da pressão de oclusão da artéria pulmonar (RANKIN, 2017).

Em felinos, as alterações cardiovasculares incluem arritmias cardíacas, como bradicardia sinusal, bloqueios atrioventriculares e taquiarritmias, especialmente quando administrada em doses elevadas (40 µg/kg, via intramuscular) (MCSWEENEY *et al*., 2012). Achados eletrocardiográficos em gatos demonstraram aumento na amplitude da onda T, porém dentro dos valores de referência, aumento do índice de tônus vasovagal e ocorrência de arritmia sinusal respiratória, sugerindo que a dexmedetomidina, na dose de 5 µg /kg, aumenta o tônus parassimpático em gatos saudáveis. Assim, deve-se considerar o risco de seu uso em pacientes suscetíveis a apresentarem bradicardia (CARVALHO *et al.*, 2019).

A concentração plasmática de dexmedetomidina está diretamente relacionada à intensidade de seus efeitos adversos, como a diminuição do índice cardíaco e o aumento da resistência vascular periférica, podendo ocasionar complicações hemodinâmicas, como hipertensão e bradicardia (PYPENDOP; HONKAVAARA; ILKIW, 2017).

Para reverter os efeitos da dexmedetomidina, utilizam-se antagonistas dos receptores α2-adrenérgicos, como a tolazolina, um antagonista não seletivo, e a ioimbina e o atipamezole, ambos seletivos para o receptor α2. O atipamezole, que apresenta maior afinidade pelos receptores α2, tem meia-vida de eliminação de cerca de 2 horas, coincidente

com a da dexmedetomidina. Esse fármaco provoca efeitos adversos mínimos, como micção, salivação e hipotensão (COTÊ *et al.*, 2022).

2.7 CONSIDERAÇÕES CLÍNICAS SOBRE A ASSOCIAÇÃO DE GABAPENTINA E DEXMEDETOMIDINA EM GATOS

A espécie felina é frequentemente desafiadora em procedimentos anestésicos devido ao seu temperamento, caracterizado por agressividade e ansiedade. Essas características exigem o uso de doses elevadas de sedativos e tranquilizantes, o que pode resultar em efeitos adversos, como depressão respiratória e cardiovascular (GRUBB *et al.*, 2020). Portanto, a formulação de protocolos anestésicos eficazes deve equilibrar cuidadosamente as dosagens dos fármacos, visando a prevenção de complicações.

A escolha de medicamentos para sedação e tranquilização de gatos, especialmente durante exames diagnósticos como ecocardiogramas, é fundamental. É necessário um controle eficaz do estresse para garantir a imobilidade adequada, sem comprometer o bem-estar do animal. Nesse cenário, a dexmedetomidina e a gabapentina se destacam como opções terapêuticas importantes, cada uma atuando em aspectos distintos do manejo comportamental e do controle da dor durante os procedimentos.

Rutherford *et al.* (2022) conduziram estudo para validação da Escala de Pontuação de Sedação Multiparamétrica Felina (EPSMF), e observaram que a administração de gabapentina antes da pré-medicação com dexmedetomidina resultou em escore de sedação de zero a sete pontos, em escala de zero a 12. Esta pontuação foi classificada como “sedação leve” na Escala Visual Analógica (EVA). Por outro lado, os animais que não receberam gabapentina apresentaram pontuação média de um ponto na EPSFM, e foram classificados como “ausência de sedação” na EVA.

Os mesmos animais que receberam gabapentina, posteriormente foram medicados com dexmedetomidina em associação com opioide, e apresentaram pontuação máxima de sedação na ESPMF (12 pontos), e classificados na EVA como “sedação profunda”. Os animais que não receberam gabapentina apresentaram pontuação de dois a 12 na ESPMF, a depender da dose de dexmedetomidina administrada (RUTHERFORD *et al.*, 2022).

Embora o uso isolado de ambos os fármacos tenha sido amplamente estudado, a combinação desses agentes em práticas clínicas, como durante a realização de ecocardiogramas, carece de dados conclusivos sobre os efeitos combinados. A

dexmedetomidina promove sedação, enquanto a gabapentina desempenha um papel relevante na atenuação da ansiedade, particularmente em felinos.

3 ARTIGO CIENTÍFICO

Os resultados da pesquisa estão apresentados na forma de artigo científico. A realização deste estudo foi aprovada pela Comissão de Ética no Uso de Animais da Universidade Federal da Fronteira Sul (CEUA/UFFS), sob protocolo de nº 1050090824 (ANEXO A). A formatação do manuscrito está de acordo com as normas do periódico "*Veterinary Anesthesia and Analgesia*" (ANEXO B).

Os requisitos da revista para submissão serão apresentados a seguir e incluem: *title page, manuscript e tables.*

3.1 TITLE PAGE

Title page

"Cardiovascular and Behavioral Effects of Dexmedetomidine Alone or Combined with Gabapentin in Healthy Cats"

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Running head: Cardiovascular and behavioral effects of dexmedetomidine and gabapentin in cats.

Authors' contributions:
MM: study design, acquisition of data, data management, preparation of manuscript, statistical analysis, data interpretation; ALRM,: acquisition of data, data management, preparation of manuscript, statistical analysis, data interpretation; AFFM: data management, statistical analysis, data interpretation, acquisition of data; PRPB: data management, data interpretation, acquisition of data; GCF: study design, data management, data interpretation, acquisition of data, supervision; TC: study design, data management, data interpretation, acquisition of data, supervision.

Acknowledgements:
The authors would like to thank the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES) for the financial support and for fostering research development, without their help the execution of this research would not have been possible

Funding:
This study was funded by the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES), Brazil.

The authors declare no conflict of interest

3.2 MANUSCRIPT

Cardiovascular and Behavioral Effects of Dexmedetomidine Alone or Combined with Gabapentin in Healthy Cats

Abstract

Objective To evaluate the sedative and cardiovascular effects of gabapentin combined with dexmedetomidine in cats.

Study design Prospective, randomized, experimental trial.

Animals Fifty-two female cats, aged 1 to 4 years, weighing 3.861 kg ± 0.576.

Methods Cats were randomly allocated to receive either gabapentin (50 mg kg^{-1}, PO; n=26) or a placebo (n=26). After 90 minutes, physiological parameters, sedation and stress scores and echocardiography were assessed. Subsequently, each group was subdivided to receive dexmedetomidine at either a low dose (GD2/PD2; n=13 per subgroup) or a high dose (GD5/PD5; n=13 per subgroup). Evaluations were repeated 30 minutes post-administration. Data analysis was performed using ANOVA for parametric data, followed by Holm post hoc tests. Significance was set at $p < 0.05$

Results The combination of gabapentin and dexmedetomidine did not significantly enhance sedation or stress reduction compared to dexmedetomidine alone, as shown by the sedation and stress scores. All groups exhibited similar increases in sedation and stress reduction over time. However, the GD5 group displayed a greater decrease in heart rate and a higher incidence of cardiac valvular regurgitation.

Conclusion and clinical relevance These findings suggest that while gabapentin did not potentiate the sedative effects of dexmedetomidine, it may have an impact on cardiovascular parameters that warrants further investigation.

Keywords Cat-friendly, sedation, drug interaction, anxiolytic, cardioprotective.

Introduction

The α-2 adrenergic receptor agonists have been widely used in veterinary medicine, particularly as adjunct anesthetics. These drugs act on α-2 adrenergic receptors, mediating inhibitory actions on norepinephrine release in the central and peripheral nervous systems (Murrel, 2017). Dexmedetomidine, a highly selective α-2 adrenergic agonist, has proven effective in providing sedation and analgesia, in addition to reducing the need for other anesthetic agents (Smith, 2017).

Its effects are dose-dependent, and it may be administered indiviadually or in combination within a dose range of 2 to 20 µg/kg to induce sedation. The maximum plasma concentration of gabapentin following intramuscular administration is observed 30 minutes after administration and remains stable until approximately 100 minutes, after which it begins to decline, with complete elimination occurring within 480 minutes (Pypendop, 2017).

Dexmedetomidine can cause diverse hemodynamic changes, such as increased vascular resistance and a decrease in heart rate, depending on the dose (Muñoz et al., 2017). Its action on presynaptic α2 receptors reduces norepinephrine release and may lead to adverse effects, such as vasoconstriction (Panzer et al., 2009). Furthermore, at high doses, dexmedetomidine can trigger biphasic pressure changes, initially increasing followed by a reduction in blood pressure and an increase in heart rate (Liu et al., 2021).

Studies have shown that dexmedetomidine may exert a direct cardioprotective effect against ischemic injury by reducing catecholamine release and modulating the sympathetic response. Additionally, it may minimize oxidative damage and apoptosis in the cardiac muscle during ischemic periods, potentially offering protection in myocardial hypoxia (Takahashi et al., 2023).

However, despite evidence of its cardioprotective effects, there is also evidence indicating that its administration induces various cardiovascular alterations, including significant reductions in heart rate, cardiac output (CO), as well as increases in systemic vascular resistance, central venous and pulmonary artery occlusion pressures (Rankin, 2017).

Dexmedetomidine is widely used for sedation in cats; however, its cardiovascular effects may influence echocardiographic variables (Slingsby et al., 2010; Santos et al. 2010). Echocardiography is essential for screening cardiac diseases such as hypertrophic cardiomyopathy (HCM), the most common cardiomyopathy in cats (Häggström, 2015). While most cats can undergo the procedure without sedation, a subset requires sedation to facilitate

the examination (Häggström, 2016). However, sedative agents may alter cardiovascular parameters, potentially affecting diagnostic accuracy (Sinclair, 2003).

Gabapentin, an anxiolytic widely used in veterinary medicine, is frequently administered to cats before transport or veterinary visits to reduce stress and facilitate handling (Van Haaften et al., 2017). Its administration at least 90 minutes before handling aligns with its peak plasma concentration, ensuring optimal therapeutic effects (Siao; Pypendop; Ilkiw, 2010). Given its widespread use for stress reduction before procedures, further investigation is needed to evaluate its efficacy as a premedication in animals undergoing sedation and anesthesia.

Gabapentin binds to the α2δ subunits of voltage-gated calcium channels, inhibiting the release of excitatory neurotransmitters, and consequently providing anxiolytic and analgesic effects. Gabapentin does not have significant direct effects on hemodynamic parameters, making it an attractive option when controlling anxiety and pain is required without compromising cardiovascular stability (Calandre; Villademoros; Slim, 2016). However, its clinical impact, particularly in combination with dexmedetomidine, should not be overlooked. The potential interactions between these drugs and their influence on cardiovascular stability need further investigation.

Additionally, by reducing the fusion of left ventricular filling waves, gabapentin improves diastolic function on echocardiographic evaluations, further supporting its potential as an anesthetic adjunct (Veronezi et al., 2022). There is only one study that has evaluated the combination of gabapentin and dexmedetomidine, demonstrating its potential to enhance sedation and analgesia (Rutherford et al., 2021).

The cardiovascular effects of α2-adrenoceptor agonists have been previously investigated in dogs and cats (Wang et al., 2016), but data on the combination of dexmedetomidine and gabapentin remain limited. This study aims to evaluate the effects of dexmedetomidine and gabapentin on sedation, stress, physiological and echocardiographic parameters in healthy cats, with the goal of optimizing anesthetic protocols and better controlling stress and physiological variables during clinical procedures.

Materials and methods

Animals

The project was carried out after approval by the Ethics Committee for the Use of Animals of the Federal University ****** (protocol number 1050090824). A total of 52 client-owned cats, with a body mass ranging from 2 to 6 kilograms (kg) and an age range of 2 to 6 years, were enrolled in the study.

Animals underwent a screening process one week prior to the experiment to ensure compliance with health and behavior criteria. The anamnesis included verification of vaccination records and the absence of reported health alterations in the preceding month. Clinical assessment required an appropriate body condition score and the absence of abnormal findings.

Cardiac evaluation consisted of electrocardiography and echocardiography, with animals exhibiting cardiopathies, arrhythmias, or conduction disorders being excluded. Stress levels were assessed using the Cat Stress Score, which evaluates facial and body expressions indicative of stress. To be included in the study, animals were required to have a stress score of ≥3, classified as "weakly tense."

Experimental design

The study was designed as a prospective, placebo-controlled, randomized experimental trial. Randomization was performed using an online randomization tool (https://randomizer.org) to ensure an equal sample size across the evaluated groups.

A priori sample size calculation (G*Power 3.1.9.7; Heinrich Heine University, Germany) was performed to ensure adequate statistical power for the study. The analysis was based on an ANOVA design for repeated measures between factors, with an effect size (f) of 0.4, an alpha error probability of 0.05, and a desired power of 0.8. The study design included four groups and three repeated measurements, with a correlation among repeated measures set at 0.5. The analysis determined a required total sample size of 52 subjects to achieve sufficient power (actual power = 0.8228) while maintaining a critical F-value of 2.79806 (Keastner et al. 2024).

Study groups

After an initial baseline evaluation, the 52 animals were initially divided into two groups, with half (n=26) receiving gabapentin (100 mg/cat) and the other half (n=26) receiving a placebo treatment. Subsequently, within the gabapentin-treated group, after 90 minutes half of the animals (n=13) received dexmedetomidine at 2 µg/kg, identified as GD2 (Gabapentin Dexmedetomidine-2 µg/kg), while the other half (n=13) received 5 µg/kg of dexmedetomidine, identified as GD5 (Gabapentin Dexmedetomidine-5 µg/kg). In the placebo-treated group, half of the animals (n=13) received dexmedetomidine at 2 µg/kg, identified as PD2 (Placebo Dexmedetomidine-2 µg/kg), and the other half (n=13) received 5 µg/kg of dexmedetomidine, identified as PD5 (Placebo Dexmedetomidine-5 µg/kg).

Gabapentin was administered orally (100 mg per cat) in a compounded gelatin capsule (size 3), containing aerosil, pre-gelatinized starch, and microcrystalline cellulose as excipients. Ninety minutes after administration (M1), physiological parameters, sedation level, and stress scores were assessed, followed by echocardiographic evaluation.

Dexmedetomidine (Dexdomitor®, 0.5 mg/mL, Zoetis, São Paulo-SP) was then administered intramuscularly (IM) into the semitendinosus muscle of the pelvic limb at a dose of 2 µg/kg in the GD2 group and 5 µg/kg in the GD5 group. Thirty minutes after dexmedetomidine administration (M2), physiological parameters, sedation level, and stress scores were reassessed, along with a second echocardiographic evaluation. Following anesthetic recovery and stabilization of physiological parameters, the animals were discharged to their homes under the care of their guardians.

Study evaluations

The evaluation time points consisted of M0 (baseline pre-medication assessment), M1 (90 minutes post-gabapentin/placebo assessment), and M2 (30 minutes post-dexmedetomidine assessment). At each time point, physiological parameters were measured, sedation and stress assessments were performed, and an echocardiographic examination was conducted.

The physiological parameters assessed included systolic arterial pressure (SAP), heart rate (HR), respiratory rate (RR), and body temperature (T°C). SAP was measured using an oscillometric device with a 9.5-MHz probe (Parks model 811-BTS, Parks Medical, Perimed, Bury St. Edmonds, UK). Measurements were performed with the animals in a sitting position under minimal restraint. A cuff with a width corresponding to approximately 40% of the forelimb circumference was placed on the antebrachium, with the arterial marker positioned

ventrally. The forelimb was maintained at heart level to ensure accuracy. Once consistent readings were obtained, BP was recorded as the mean of three consecutive measurements. All measurements were performed by the same examiner.

Sedation was assessed using the Feline Multiparameter Sedation Score (FMSS) (Rutherford et al., 2022). This sedation scale evaluated posture, behavior, and responsiveness to sounds and handling during restraint, injection, or intravenous catheter placement. A score was assigned to each of these parameters, ranging from zero to three, with a maximum total score of 12, representing the highest level of sedation, and a minimum score of zero, indicating the absence of sedation.

The Cat Stress Score (CSS) was used to assess stress levels in the felines. The CSS classified stress into seven levels by observing body posture, abdomen, hind limbs, tail, head, eyes, pupils, ears, vibrissae, and vocalization, ranging from 1 (fully relaxed) to 7 (terrorized) (Pankratz et al., 2018). All evaluations were performed by two trained assessors who were blinded to the treatment protocols.

All echocardiographic assessments were performed by an experienced professional, blinded to the cat's identity and sedation status. Echocardiography was conducted using a SonoSite M-TURBO® ultrasound system (Fujifilm, Bothell, USA) equipped with a sector transducer. The animals were placed in lateral recumbency on a specialized cushion to ensure stability, minimize stress, and optimize image acquisition. A conductive gel was applied to enhance acoustic coupling. All examinations adhered to the guidelines established by the Echocardiography Committee of the Cardiology Specialty of the American College of Veterinary Internal Medicine (Acierno et al., 2018).

Echocardiographic evaluation was conducted to assess cardiac morphology, hemodynamics, and functional parameters. Morphological parameters included interventricular septal thickness in diastole (IVSd) and systole (IVSs), left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), as well as posterior left ventricular wall thickness in diastole (PLd) and systole (PLs). Additionally, left atrial diameter (LA), aortic diameter (Ao), and the left atrium-to-aorta ratio (LA/Ao) were measured to assess structural cardiac dimensions.

Hemodynamic parameters were evaluated using pulsed-wave Doppler, encompassing pulmonary acceleration time (AT), ejection time (ET), and the AT/ET ratio, along with pulmonary cardiac output (COp), pulmonary heart rate (HRp), pulmonary velocity-time integral (VTIp), and pulmonary peak velocity (PVp). Additionally, aortic hemodynamic parameters, including aortic cardiac output (COAo), aortic heart rate (HRAo), aortic velocity-

time integral (VTIAo), and aortic peak velocity (PVAo), were also assessed. Transmitral flow was assessed through the E and A waves and the E/A ratio, while isovolumetric relaxation time (IVRT) was measured in an apical five-chamber view.

Functional parameters were determined through M-mode and tissue Doppler imaging, including left ventricular shortening fraction (LVSF) and ejection fraction (LVEF) to evaluate systolic function. Pulsed tissue Doppler imaging (TDI) at the mitral valve insertion site provided early diastolic myocardial velocity (E'), late diastolic myocardial velocity (A'), systolic myocardial velocity (S'), and the A'/E' ratio. Additionally, tricuspid annular plane systolic excursion (TAPSE) and mitral annular plane systolic excursion (MAPSE) were measured to assess longitudinal myocardial function.

Imaging was initiated from the right parasternal window, utilizing a cross-sectional view at the level of the LV and the chordae tendineae. M-mode echocardiography was employed to measure IVSd, IVSs, LVEDD, LVESD, PLd, and PLs. Additionally, LVSF and LVEF were calculated to assess systolic function (Madron, 2016a).

Subsequently, in two-dimensional mode, a right parasternal short-axis view at the level of the aortic valve was utilized to assess LA, Ao, and LA/Ao, following the methodology described by Selmi et al. (2003). Ao measurements were obtained by tracing a line from the junction of the aortic wall with the non-coronary and left coronary aortic cusps, extending to the free atrial wall to determine the LA dimension.

Transpulmonary flow was evaluated using pulsed-wave spectral Doppler, aligning the ultrasound beam between the pulmonary valve leaflets in a cross-sectional view to determine maximum flow velocity, as described by Madron (2016a). Additional parameters, including AT, ET, and the AT/ET ratio, were measured following the methodology established by Chetboul (2016a). Furthermore, COp, HRp, VTIp, and PVp were also assessed. In the longitudinal section, IVSd, IVSs, PLd, PLs, LAd, and LAs were measured according to the protocol proposed by Freeman et al. (2015).

In the left parasternal region, the transmitral flow was evaluated in the apical four-chamber view, using pulsed Doppler to obtain the E, A waves, and the E/A ratio (Afonso and Reis, 2012). The Doppler beam was then positioned in an apical five-chamber view to simultaneously assess aortic and mitral valve flows, enabling the measurement of IVRT (Madron, 2016a). Pulsed TDI was performed at the mitral valve insertion site on the LV free wall using an apical four-chamber view. This facilitated the acquisition of E', A', S', and the A'/E' ratio, as outlined by Chetboul (2016b). Additionally, COAo, HRAo, and VTIAo were assessed to evaluate the hemodynamic performance of the aorta.

TAPSE was measured during systole by tracking the movement of the tricuspid annulus throughout the cardiac cycle. The distance between the basal and apical positions of the tricuspid annulus was recorded during systole, capturing the maximum excursion. Similarly, MAPSE was assessed using an apical four-chamber view, focusing on the mitral valve. The mitral annular motion was measured during systole, recording the excursion towards the apex of the LV. Both measurements were obtained using two-dimensional imaging, ensuring clear baseline alignment and evaluation of the maximum movement of the tricuspid and mitral annuli.

Statistical analysis

Data were analyzed using JASP software (version 0.19.1). Normality was assessed using the Shapiro-Wilk test. Different statistical tests were applied depending on the nature of the data to evaluate the effects of gabapentin and dexmedetomidine on the measured parameters. Comparisons between time points (M0, M1, and M2) within each group (GDA, GDB, PDA, PDB) were performed using repeated measures ANOVA, followed by Holm post hoc tests for multiple comparisons when applicable. When the assumptions of normality or sphericity were not met, the Friedman test was applied, followed by Conover's post hoc test.

Normally distributed data were expressed as mean ± standard deviation (SD), whereas non-normally distributed data were reported as median (minimum;maximum). A significance level of $p < 0.05$ was considered for all analyses.

Results

Animals

The study was conducted on 52 adult mixed-breed cats (21 males and 31 females), all deemed clinically healthy based on physical examination and laboratory tests. The mean body weight was 3.8 ± 0.59 kg, and the mean age was 3.9 ± 1.1 years. The mean gabapentin dose administered was 26.8 ± 4.5 mg/kg.

Physiological Parameters

The mean values of all physiological parameters analyzed at baseline (M0), after gabapentin administration (M1), and following sedation with dexmedetomidine (M2) are presented in Table 1. SAP did not differ significantly at any time point across groups ($p = 0.0885$). Post hoc analyses further confirmed that there were no significant increase or decrease in SAP within any group at different evaluation time points.

There was a significant effect of time on HR ($p < 0.001$), indicating variation in HR over time. Post hoc analyses revealed that, within the GD5 group, HR significantly decreased between M0 (209.769 ± 34.661) and M2 (132.154 ± 40.129) ($p < 0.001$). A significant reduction in HR was also observed between M1 (198.615 ± 26.120) and M2 (132.154 ± 40.129) ($p < 0.001$) in the GD5 group. In the GD2 group HR significantly decreased from M0 (208.615 ± 41.7) to M2 (152.769 ± 25.054) ($p < 0.001$). In the same group, significant reduction ($p < 0.001$) was also observed between M1 (208.923 ± 39.367) and M2 (152.769 ± 25.054).

Post hoc analyses for the PD5 group showed that HR significantly decreased from M0 (213.85 ± 33.817) to M2 (162.154 ± 28.653) ($p = 0.005$). Similarly, a significant HR reduction was observed from M1 (211.538 ± 37.257) to M2 (162.154 ± 28.653) ($p = 0.003$,). In the PD2 group, HR significantly decreased between M0 (206 ± 25.652) and M2 (140.615 ± 42.828) ($p < 0.001$). Additionally, a significant reduction was observed between M1 (187.769 ± 37.586) and M2 (140.615 ± 42.828) ($p < 0.001$).

At M0 and M1, no animals exhibited HR values below the physiological reference range. However, at M2, bradycardia was observed in 46.15% (6/13) of cats in the GD5 group, 30.76% (4/13) in the PD2 group, and 7.69% (1/13) in both the GD2 and PD5 groups.

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Regarding fR assessments, a significant effect of time was observed ($p < 0.001$, $\eta^2p = 0.343$), indicating variations in fR over the evaluation periods. However, the time*group interaction was not significant ($p = 0.160$), suggesting that all groups exhibited a similar pattern of fR changes across the different time points.

Post hoc analyses revealed a significant reduction in fR within the GD5 group, decreasing from M0 (68 [48;180]) to M2 (41.154 ± 9.848) ($p < 0.001$). Similarly, in the GD2 group, fR significantly decreased from M1 (61.538 ± 17.553) to M2 (40.769 ± 6.085) ($p < 0.001$). In the PD5 group, fR also showed a significant reduction from M1 (64.796 ± 32.265) to M2 (36 [24;96]) ($p < 0.002$).

Stress and Sedation Assessment

Regarding the CSS evaluations (Fig. 1), the average score from both evaluators was used for statistical analysis. A significant effect of time was observed ($p < 0.001$, $\eta^2p = 0.778$), indicating fluctuations in CSS over the evaluation periods. However, the time*group interaction was not significant ($p = 0.334$), suggesting that CSS followed a similar pattern of variation across all groups.

Post hoc analyses revealed a significant decrease in CSS scores within the GD5 group, with scores decreasing from M0 (4 [3;5,5]) to M2 (1.5 [1;4]) ($p < 0.001$). A similar decrease was observed when comparing M1 (3,5 [2;5]) to M2 (1.5 [1;4]), with $p < 0.001$. In the GD2 group, significant differences in CSS scores were found when comparing M0 (4 [3;5,5]) to M1 (3 [2;4,5]), M0 (4 [3;5,5]) to M2 (2 [1;3]), and M1 (3 [2;4,5]) to M2 (2 [1;3]), with $p < 0.001$ for all comparisons.

Post-hoc analyses of the PD5 group's CSS scores revealed a significant decrease ($p < 0.001$) from M0 (4 [4;5]) to M2 (2 [1.5;3]), as well as from M1 (3,5 [3;4,5]) to M2 (2 [1.5;3]). In the PD2 group, significant reductions in CSS scores were also observed, with differences between M0 (4 [2,5;5,5]) and M1 (3 [2;5]) ($p = 0.006$), as well as between M0 (4 [2,5;5,5]) and M2 (1,5 [1;3]), and M1 (3 [2;5]) and M2 (1.5 [1;3]), with $p < 0.001$.

Regarding the FMSS scores (Fig. 2), the average scores from both evaluators were used for statistical analysis. A significant effect of time was observed ($p < 0.001$, $\eta^2p = 0.705$), indicating fluctuations in FMSS scores over the evaluation periods. However, the time*group interaction was not significant ($p = 0.290$), suggesting that FMSS scores followed a similar pattern of variation across all groups.

Post-hoc analyses revealed a significant increase ($p < 0.001$) in FMSS scores within the GD5 group from M0 (0 ± 0) to M2 (5.192 ± 4.065), and from M1 (0 [0;2]) to M2 (5.192 ± 4.065). In the GD2 group, significant increase ($p < 0.001$) was observed between M0 (0 ± 0) and M2 (5.731 ± 3.580), as well as between M1 (0 [0;4]) and M2 (5.731 ± 3.580).

In the PD5 group, post-hoc analyses revealed significant increases in FMSS scores between M0 (0 [0;0.5]) and M2 (7 [0;12]) ($p = 0.028$). A similar significant increase was observed when comparing M1 (0 [0;1]) to M2 (7 [0;12]) ($p = 0.025$). In the PD2 group, significant increases in FMSS scores were also observed ($p < 0.001$) between M0 (0 [0;1]) and M2 (7,5 [0;12]) , as well as between M1 (0 [0;3.5]) and M2 (7,5 [0;12]) in the post-hoc analyses.

Echocardiographic Assessment

No instances of regurgitation were recorded at M0 or M1. In M2, regurgitation was observed in 61.54% of animals in the GD5 group (n = 8/13), 27.7% in the PD5 group (n = 3/13), 27.07% in the GD2 group (n = 3/13), and 30.76% in the PD2 group (n = 4/13). The regurgitations involved the mitral, tricuspid, pulmonary, and aortic valves. Some animals exhibited regurgitation in a single valve, while others presented multiple regurgitation sites.

In the PD5 group, all three affected animals exhibited isolated regurgitation at a single valve. Conversely, in the GD5 group, all eight affected animals presented multiple regurgitation sites, with some individuals exhibiting up to three regurgitation foci (Figure 1.). In the GD2 and PD2 groups, both isolated and multiple regurgitation foci were observed.

The chi-square test used to assess the association between bradycardia and echocardiographic valvular regurgitation yielded a *p*-value of 0.06, indicating a trend toward association, although not statistically significant at the 5% level.

In the echocardiographic evaluation, encompassing the assessment of morphology, hemodynamics, and functional parameters, no statistically significant differences were observed between the groups or across the time points of evaluation, using Two-way ANOVA tests. However, post hoc analyses revealed some differences in specific echocardiographic parameters, suggesting potential variations that were not evident in the overall statistical comparisons.

Regarding the morphological assessments in the echocardiographic evaluation (Table 2), post hoc analyses revealed statistically significant differences in the LA measurements in the GD5 group between M1 (0.823 ± 0.114) and M2 (0.875 [0.64; 0.96]) ($p < 0.001$).

In the post hoc analyses related to the cardiac hemodynamics (Table 3), significant increase in ET was observed in the GD5 group, from M0 (152.692 ± 23.507) to M2 (214.583 ± 34.605), as well as from M1 (171.923 ± 13.775) to M2 (214.583 ± 34.605) ($p < 0.01$). In the GD2 group, a significant increase in ET was observed between M1 (157.917 ± 19.242) and M2 (198.846 ± 44.260) ($p = 0.046$). The PD5 group also showed a significant increase in ET between M1 (160 [90;180]) and M2 (193.462 ± 35.904) ($p = 0.023$). Finally, the PD2 group exhibited a significant increase in ET from M0 (165 [145;215]) to M2 (209.231 ± 34.752) and from M1 (155 [135;210]) to M2 (209.231 ± 34.75 2) ($p = 0.02$).

Regarding the behavior of the AT/ET ratio in the post hoc evaluations, a significant increase was observed in the GD5 group, from M0 (90 ± 21.311) to M2 (159.5 ± 41.194), as

well as from M1 (109.231 ± 14.698) to M2 (159.5 ± 41.194) ($p < 0.01$). The GD2 group also showed an increase in the AT/ET ratio between M0 (98.846 ± 23.818) and M2 (135.385 ± 38.104), as well as from M1 (89.167 ± 19.404) to M2 (135.385 ± 38.104) ($p = 0.014$). The PD5 group exhibited a significant increase ($p = 0.025$) between M1 (88.273 ± 24.409) and M2 (135.833 ± 30.833).

COp showed a significant decrease in the post hoc analysis for the PD5 group, from M0 (0.615 ± 0.230) to M2 (0.382 ± 0.140) ($p = 0.021$). HRp showed a significant reduction in the post hoc analysis for the GD5 group, from M0 (188.167 ± 35.698) to M2 (108 [86; 230]), as well as from M1 (185.769 ± 27.332) to M2 (108 [86; 230]) ($p = 0.02$ and $p = 0.007$, respectively). In the PD2 group, a reduction was observed (pH = 0.011) between M0 (195.385 ± 36.705) and M2 (141 ± 42.610).

A significant reduction in the HRAo post hoc analysis for the GD5 group was observed, from M0 (185.250 ± 32.844) to M2 (124.231 ± 36.111), as well as from M1 (187.154 ± 24.474) to M2 (124.231 ± 36.111) ($p < 0.001$). In the GD2 group, a significant decrease was observed between M1 (208 ± 25.902) and M2 (208 ± 25.902) ($p < 0.001$). The PD2 group also showed a significant reduction from M0 (192.769 ± 32.262) to M2 (146.538 ± 47.006), as well as from M1 (197.615 ± 39.761) to M2 (146.538 ± 47.006) ($p < 0.001$).

Functional parameters (Table 3) post hoc analyses, revealed a statistically significant reduction in LVSF within the GD2 from M0 (58.723 ± 11.302) to M2 (46.227 ± 12.196) and also from M1 (52,438 ± 9,756) to M2 (46.227 ± 12.196) ($p = 0.017$ and $p = 0.016$, respectively).

Discussion

In the analysis of physiological parameters, systolic arterial pressure (SAP) remained stable across time points and groups, indicating that the combination of dexmedetomidine and gabapentin did not induce significant hemodynamic alterations. Previous studies have demonstrated that α2-agonists, such as dexmedetomidine, can increase blood pressure post-sedation due to a time-dependent rise in systemic vascular resistance (Monteiro et al., 2009).

However, it has also been reported that low doses of dexmedetomidine may not cause substantial changes in SAP, supporting our findings that no significant alterations in SAP were observed in cats that received dexmedetomidine (Selmi et al., 2003; Lamont et al., 2001). This

lack of change in SAP suggests that, in the doses used in our study, dexmedetomidine alone may not induce marked hemodynamic shifts.

Furthermore, since no significant alterations in SAP were observed in cats receiving the combination of dexmedetomidine and gabapentin, it is likely that gabapentin does not potentiate or significantly modify the cardiovascular effects of dexmedetomidine. Given gabapentin's primary mechanism of action, which involves calcium channel modulation and central nervous system depression (Adrian et al., 2018), suggesting that a single oral dose of gabapentin doesn't appear to have any direct or indirect impact on blood pressure. Therefore, these findings suggest that gabapentin does not have the potential to alter or exacerbate changes in blood pressure induced by dexmedetomidine.

fR significantly decreased over time, but no significant interaction between time and group was found, indicating a uniform reduction across groups. However, HR showed significant variation over time, although the time*group interaction was not significant, indicating that all groups exhibited a similar HR reduction pattern. Notably, HR significantly decreased within all groups from baseline (M0) to post-dexmedetomidine administration (M2).

When comparing the groups PD5 to GD5, a greater HR reduction was observed in the GD5 group at M2. Additionally in both groups, the same dose of dexmedetomidine was administered; however, the incidence of bradycardia was markedly higher in the GD5 group (46.15%) compared to the PD5 group (7.69%). Given that the only difference between these protocols was the inclusion of gabapentin in the GD5 group, the authors hypothesize that the higher incidence of HR reduction in this group may be attributed to the pharmacological interaction between gabapentin and dexmedetomidine.

This finding implies that gabapentin may enhance the bradycardic effect of dexmedetomidine, although the reduction in HR remained within physiological limits for the species. The decrease in HR post-sedation was significant. Bradycardia has been widely reported in several studies involving α2-agonists in cats (Selmi, 2003; Monteiro, 2009); and gabapentin has also been associated with reductions in HR (Chen et al., 2019). Therefore, the observed decrease in HR is likely attributable to the combined effects of both drugs.

Gabapentin has been shown to significantly improve owners' perceptions of their cats' stress when administered prior to a veterinary visit (Van Haaften et al., 2017). However, in the present study, the evaluation of the Cat Stress Score (CSS) revealed that pre-administration of gabapentin did not significantly reduce the CSS from baseline to M2, nor did it influence dexmedetomidine-induced sedation. While a significant reduction in stress scores was

observed over time across all experimental groups, regardless of prior gabapentin administration, no significant interaction between time and group factors was found. These results are consistent with those of Lombaert et al. (2023), who reported that treatment with gabapentin was not associated with significantly lower stress scores or improved compliance in cats.

In the groups that did not receive gabapentin (PD5 and PD2), the reduction in CSS scores was similar to that observed in the groups that received the combination of gabapentin and dexmedetomidine (GD5 and GD2). This indicates that gabapentin, when administered before hospital sedation with dexmedetomidine, did not significantly potentiate its sedative effects. These findings are of great clinical relevance, as they suggest that the use of gabapentin as a premedication for hospital sedation may not provide additional benefits in terms of stress reduction or enhancement of dexmedetomidine-induced sedation.

Furthermore, the results reinforce the efficacy of dexmedetomidine alone in reducing stress in cats, with significant decreases in CSS regardless of the dose used. The similarity between the groups that received high and low doses of dexmedetomidine (PD5 and PD2) and the groups that received gabapentin (GD5 and GD2) suggests that the action of dexmedetomidine on α2-adrenergic receptors was sufficient to promote the expected sedation without additional influence from gabapentin.

The analysis of FMSS scores revealed significant increases in sedation scores from M0 to M2 across all groups. However, no significant differences were observed between groups at M2, indicating that the addition of gabapentin to dexmedetomidine did not significantly enhance sedation compared to dexmedetomidine alone.

The PD2 group exhibited the highest FMSS scores, reflecting more pronounced sedation. In contrast, animals in the GD2 and GD5 groups, which received pre-treatment with gabapentin, demonstrated a significant increase in FMSS scores from M0 to M2. Although these increases were significant, they were less pronounced when compared to the PD2 group, suggesting a lesser effect of gabapentin on sedation.

These findings indicate that gabapentin did not potentiate the sedative effects of dexmedetomidine. While both dexmedetomidine and the combination with gabapentin resulted in increased sedation, the absence of a significant difference between groups at M2 suggests that the addition of gabapentin did not exacerbate the sedative effect.

In the current study, the dose of gabapentin administered (100 mg per cat) may not have been sufficient to produce a noticeable synergistic effect when combined with dexmedetomidine, as indicated by the observed results in CSS and FMSS. Commonly used

oral single doses of gabapentin range from 50 to 150 mg per cat, with higher doses generally producing more pronounced sedative effects in most cats (Pankratz et al., 2018; Van Haaften et al, 2017; Allen et al., 2021). Given that the dose chosen in our study was considered intermediate based on existing literature, it is plausible that a higher dose could alter the pharmacological interaction between gabapentin and dexmedetomidine, potentially enhancing the sedative or anxiolytic effect.

In the present study, no regurgitation sites were observed at M0 or M1, which aligns with the findings of Veronezi et al. (2022). The authors reported that gabapentin did not induce cardiac regurgitation in their study population and concluded that it did not significantly alter the physiological or echocardiographic variables analyzed. Thus, gabapentin was not associated with significant cardiovascular hemodynamic changes in healthy young cats.

However, when comparing the incidence of cardiac regurgitation between the GD5 and PD5 groups in our study, we observed that the prevalence in GD5 was more than twice that recorded in PD5. Since both groups received the same dose of dexmedetomidine, but GD5 was premedicated with gabapentin whereas PD5 received a placebo, we hypothesize that the pharmacological interaction between gabapentin and dexmedetomidine contributed to the marked increase in valvular regurgitation. These findings suggest that gabapentin may potentiate cardiac alterations when combined with dexmedetomidine.

Furthermore, as noted by Veronezi et al. (2022), it is common for cat owners to administer gabapentin at home approximately 90 minutes before a veterinary appointment to mitigate stress associated with the hospital environment and handling. However, considering our findings on the cardiac changes attributed to the interaction between gabapentin and dexmedetomidine, caution should be exercised when administering dexmedetomidine in a clinical setting to animals that have been premedicated with gabapentin at home.

Although the association between bradycardia and echocardiographic valvular regurgitation was not statistically significant ($p = 0.06$), the borderline p-value suggests a potential trend that may hold clinical relevance. It is possible that reduced heart rate could influence valvular dynamics, potentially contributing to mild regurgitation, particularly under pharmacologically induced hemodynamic alterations. Further studies with larger sample sizes are warranted to clarify this possible relationship.

The results show that in the GD5 group, the IVSd was significantly higher compared to the PD5 group at M2, with a p-value of 0.037, indicating a notable increase in diastolic

interventricular septal thickness in the group receiving gabapentin. Additionally, the IVSs was also significantly higher in the GD5 group compared to the PD5 group, with a p-value of 0.002, suggesting that the addition of gabapentin to the dexmedetomidine regimen may have contributed to an increase in systolic interventricular septal thickness as well. These findings are consistent with previous literature indicating that gabapentin can cause an increase in IVSd (Tuleski et al., 2022).

However, despite the significant increase in IVSd observed in the GD5 group, the values did not exceed the threshold for diagnosing hypertrophic cardiomyopathy (HCM) in cats, which requires an IVSd or LVWd > 0.6 cm (Freeman et al., 2015). This suggests that while gabapentin may influence myocardial dimensions, it did not induce structural changes consistent with HCM in this study. The increase in IVSd in the GD5 group could be related to a potential effect of gabapentin on cardiovascular hemodynamics or myocardial contractility, although the exact mechanisms remain unclear.

In our study, a significant reduction in fractional shortening (FS) was observed within the GD2 group when comparing baseline (M0) to M1 and M2. FS is a well-established index for assessing ventricular systolic function; however, it has limitations, particularly in being influenced by pre and post-load factors (Madron, 2016). Unlike previous studies, where changes in left ventricular systolic diameter (LVDs) and increased afterload contributed to reduced FS, our results did not show significant alterations in LVDs or increases in afterload.

The observed decrease in FS in the present study is likely attributable to the pharmacological effects of the administered drugs rather than changes in cardiac preload or afterload. These findings are consistent with those reported by Allen et al. (2021), who also observed a reduction in FS in animals receiving gabapentin, as well as by Wang et al. (2016), who documented a similar effect following dexmedetomidine administration.

Given that both drugs have been associated with a decrease in FS, we hypothesize that the combination of dexmedetomidine and gabapentin in our study may have further accentuated this reduction. Notably, while the GD2 group demonstrated a significant decrease in FS, all groups exhibited a similar trend, suggesting that the sedative protocol had a generalized effect on cardiac function across all groups.

No significant changes were observed in aorta (Ao), left atrium (LA), and LA/Ao measurements, which aligns with previous research. Kellihan et al. (2003) reported no alterations in these parameters with the use of dexmedetomidine in dogs, and Johard et al. (2018) found no changes in LA and aorta measurements in cats following dexmedetomidine and buprenorphine administration. While a statistically significant difference in LA

measurements was noted in the GD5 group between M1 and M2, this change was minimal and is unlikely to be clinically relevant. Thus, the results suggest that the protocol used did not significantly impact these cardiovascular structures.

Dexmedetomidine is known to induce a dose-dependent decrease in cardiac output (Wang et al., 2015), which aligns with our findings. In the present study, the group that received the higher dose of dexmedetomidine (PD5) exhibited a significant reduction in COp at M2 compared to the lower-dose dexmedetomidine group (PD2), at the same evaluation moment. Furthermore, in the groups that received gabapentin (PD5 and PD2), no significant changes in COp were observed following its administration, corroborating previous reports that gabapentin does not affect this echocardiographic parameter (Siepmann et al., 2025).

However, as these same animals also did not exhibit significant alterations in COp after dexmedetomidine administration, despite receiving the same dexmedetomidine doses respectively, our findings suggest a potential interaction between dexmedetomidine and gabapentin in the stabilization of COp, attenuating the expected reduction. Further studies are needed to explore this hypothesis.

The results of this study should be interpreted in view of several limitations. First, the sample includes only healthy cats, which may limit the generalization of the results to felines with pre-existing cardiovascular diseases. Additionally, the potential effects of individual variability on the level of sedation and cardiovascular response should be acknowledged, as these factors could influence the overall outcomes. Another limitation is that stress and sedation assessments were performed prior to the echocardiogram. Given that the echocardiographic procedure involved significant handling, the animals exhibited more pronounced signs of stress, which were not accounted for in the study's evaluations. Further research involving a broader population is necessary to better understand the full range of effects of dexmedetomidine and gabapentin in different clinical contexts.

Conclusions

The combination of gabapentin and dexmedetomidine did not significantly enhance sedation or stress reduction compared to dexmedetomidine alone, as evidenced by the similar outcomes in Cat Stress Score (CSS) and Feline Multiparametric Sedation Scale (FMSS) across groups. However, the GD5 group exhibited a greater heart rate reduction and a higher

incidence of cardiac valvular regurgitation, indicating potential cardiovascular effects compared to the PD5 group.

While no significant changes in systolic arterial pressure (SAP) or cardiac output (COp) were observed, the interaction between gabapentin and dexmedetomidine potentiated the bradycardic effect. These findings suggest that gabapentin may impact cardiovascular parameters without potentiating sedation, highlighting the need for further investigation into the mechanisms underlying these changes and their clinical relevance in veterinary anesthesia.

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3.3 TABLES

Table 1 – Values for systolic blood pressure (SBP), heart rate (HR) and respiratory rate (fR) of healthy cats divided in group GD2 (Gabapentin Dexmedetomidine Low), GD5 (Gabapentin Dexmedetomidine High), PD2 (Placebo Dexmedetomidine Low) and PD5 (Placebo Dexmedetomidine High), during the basal evaluation (M0), after placebo/gabapentin administration (M1) and after dexmedetomidine in low or high dose (M2).

		Group			
Variable	**Moment**	**PD2**	**PD5**	**GD2**	**GD5**
SBP	M0	128,769 ± 15,589^{Aa}	130,077 ± 25,660^{Aa}	120 (100;190)^{Aa}	127,462 ± 17,140^{Aa}
	M1	122,385 ± 16,143^{Aa}	120 (106;204)^{Aa}	129,692 ± 13,437^{Aa}	118,007 ± 12,835^{Aa}
	M2	110 (90;142)^{Aa}	110 (94;170)^{Aa}	120 (100;130)^{Aa}	111,308 ± 13,708^{Aa}
HR	M0	206 ± 25,652^{Aa}	213,85 ± 33,817^{Aa}	208,615 ± 41,7^{Aa}	209,769 ± 34,661^{Aa}
	M1	187,769 ± 37,586^{Aa}	211,538 ± 37,257^{Aa}	208,923 ± 39,367^{Aa}	198,615 ± 26,120^{Aa}
	M2	140,615 ± 42,828^{Ab}	162,154 28,653^{Ab}	152,769 ± 25,054^{Ab}	132,154 ± 40,129^{Ab}
fR	M0	60 (36;120)^{Aa}	65,538 ± 30,212^{Aab}	64,615 ± 20,516^{Aab}	68 (48;180)^{Aa}
	M1	53,231 ± 13,797^{Aa}	64,796 ± 32,265^{Aa}	61,538 ± 17,553^{Aa}	55,385 ± 12,285^{Aab}
	M2	47,385 ± 20,139^{Aa}	36 (24;96)^{Ab}	40,769 ± 6,085^{Ab}	41,154 ± 9,848^{Ab}

SBP, Sistolyc blood pressure; HR, Heart rate; fR, respiratory rate. The significance level *p*-value < 0.05. *Significant difference. Parametric variables are expressed as mean ± standard deviation and non-parametric variables are presented as median and (maximum;minimum). Capital letters (A and B) indicate statistical differences between groups within the same time point. Identical capital letters signify no significant difference ($p > 0.05$), while different capital letters denote a significant difference ($p < 0.05$). Lowercase letters (a and b) represent differences between time points within the same group. Identical lowercase letters indicate no significant difference ($p > 0.05$), while different lowercase letters indicate a significant difference ($p < 0.05$). Combination of lowercase letters (ab) indicates that the time point did not differ significantly from both previous and subsequent time points.

Table 2 – Echocardiographic morphological variables in healthy cats from different experimental groups. GDA (gabapentin and high-dose dexmedetomidine), PDB (placebo and low-dose dexmedetomidine), GDB (gabapentin and low-dose dexmedetomidine), and PDA (placebo and high-dose dexmedetomidine). Measurements were obtained at baseline (M0), 90 minutes after gabapentin or placebo administration (M1), and 15 minutes after dexmedetomidine administration (M2). Data are presented as mean ± standard deviation or median (maximum;minimum).

		Group			
Variable	**Moment**	**GD5**	**PD2**	**GD2**	**PD5**
Ao	M0	0,907 ± 0,118^{Aa}	0,852 ± 0,102^{Aa}	0,815 ± 0,127^{Aa}	0,869 ± 0,133^{Aa}
	M1	0,823 ± 0,114^{Aa}	0,811 ± 0,092^{Aa}	0,858 ± 0,082^{Aa}	0,855 ± 0,099^{Aa}
	M2	0,875 (0,64;0,96)^{Aa}	0,81 (0,71;1,07)^{Aa}	0,827 ± 0,146^{Aa}	0,868 ± 0,126^{Aa}
LA	M0	1,088 ± 0,063^{Aa}	1,088 ± 0,130^{Aa}	1,028 ± 0,131^{Aa}	1,113 ± 0,131^{Aa}
	M1	1,020 ± 0,134^{Aa}	1,0018 ± 0,131^{Aa}	1,086 ± 0,107^{Aa}	1,062 ± 0,108^{Aa}
	M2	1,17 (0,89;1,26)^{Aa}	1,095 ± 0,120^{Aa}	1,099 ± 0,121^{Aa}	1,168 ± 0,179^{Ab}
LA/Ao	M0	1,219 ± 0,176^{Aa}	1,286 ± 0,135^{Aa}	1,274 ± 0,118^{Aa}	1,294 ± 0,115^{Aa}
	M1	1,280 ± 0,179^{Aa}	1,265 ± 0,179^{Aa}	1,278 ± 0,152^{Aa}	1,255 ± 0,156^{Aa}
	M2	1,375 ± 0,113^{Aa}	1,318 ± 0,115^{Aa}	1,35± 0,148^{Aa}	1,35 ± 0,14^{Aa}
IVSd	M0	0,459 ± 0,066^{Aa}	0,446 ± 0,113^{Aa}	0,410 (0,33; 0,74)^{Aa}	0,459 ± 0,056^{Aa}
	M1	0,445 ± 0,061^{Aa}	0,461 ± 0,061^{Aa}	0,448 ± 0,049^{Aa}	0,472 ± 0,063^{Aa}
	M2	0,461 ± 0,130^{Aa}	0,429 ± 0,07^{Aa}	0,446 ± 0,105^{Aa}	0,455 ± 0,066^{Aa}
LVEDD	M0	1,413 ± 0,175^{Aa}	1,32 (1,13;1,65)^{Aa}	1,371 ± 0,238^{Aa}	1,309 ± 0,196^{Aa}
	M1	1,405 ± 0,128^{Aa}	1,381 ± 0,31^{Aa}	1,377 ± 0,171^{Aa}	1,4 ± 0,22^{Aa}
	M2	1,457 ± 0,14^{Aa}	1,512 ± 0,201^{Aa}	1,314 ± 0,249^{Aa}	1,518 ± 0,285^{Aa}
PLd	M0	0,472 ± 0,095^{Aa}	0,476 ± 0,07^{Aa}	0,533 ± 0,109^{Aa}	0,490 ± 0,083^{Aa}
	M1	0,480 ± 0,046^{Aa}	0,5 (0,35;0,52)^{Aa}	0,48 ± 0,77^{Aa}	0,48 (0,39;0,72)^{Aa}
	M2	0,502 ± 0,130^{Aa}	0,43 (0,37;0,63)^{Aa}	0,478 ± 0,096^{Aa}	0,465 ± 0,054^{Aa}
IVSs	M0	0,721 ± 0,135^{Aa}	0,681 ± 0,079^{Aa}	0,92 ± 0,144^{Aa}	0,746 ± 0,167^{Aa}
	M1	0,704 ± 0,1^{Aa}	0,750 ± 0,067^{Aa}	0,756 ± 0,159^{Aa}	0,61 (0,52;1,23)^{Aa}
	M2	0,617 ± 0,09^{Aa}	0,50 (0,48;0,89)^{Aa}	0,59 (0,41;0,91)^{Ab}	0,67 (0,59;0,97)^{Aa}
LVESD	M0	0,644 ± 0,125^{Aa}	0,684 ± 0,231^{Aa}	0,568 ± 0,19^{Aa}	0,553 ± 0,19^{Aa}
	M1	0,645 ± 0,128^{Aa}	0,52 (0,39;1,15)^{Aa}	0,546 ± 0,141^{Aa}	0,616 ± 0,224^{Aa}
	M2	0,813 ± 0,127^{Aa}	0,862 ± 0,203^{Aa}	0,812 ± 0,329^{Ab}	0,775 ± 0,176^{Ab}
PLs	M0	0,721 ± 0,146^{Aa}	0,688 ± 0,127^{Aa}	0,768 ± 0,105^{Aa}	0,774 ± 0,144^{Aa}
	M1	0,730 ± 0,066^{Aa}	0,695 ± 0,113^{Aa}	0,738 ± 0,131^{Aa}	0,772 ± 0,125^{Aa}
	M2	0,696 ± 0,134^{Aa}	0,628 ± 0,083^{Aa}	0,671 ± 0,151^{Aa}	0,703 ± 0,089^{Aa}

SIVd, interventricular septum in diastole; LVd, left ventricular diameter in diastole; EVDs, left ventricular diameter in systole; PLd, free wall in diastole; LA, left atrium; LA/Ao, left atrium and aorta ratio; IVSd. interventricular septal thickness in diastole; IVSs interventricular septal thickness in systole; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PLd, posterior left ventricular wall thickness in diastole; PLs, posterior left ventricular wall thickness in systole (PLs); LA, left atrial diameter; Ao, aortic diameter; LA/Ao, left atrium-to-aorta ratio. Capital letters (A and B) indicate statistical differences between groups within the same time point. Identical capital letters signify no significant difference ($p > 0.05$),

while different capital letters denote a significant difference ($p < 0.05$). Lowercase letters (a and b) represent differences between time points within the same group. Identical lowercase letters indicate no significant difference ($p > 0.05$), while different lowercase letters indicate a significant difference ($p < 0.05$). Combination of lowercase letters (ab) indicates that the time point did not differ significantly from both previous and subsequent time points.

Table 3 – Echocardiographic hemodynamics variables in healthy cats from different experimental groups. GDA (gabapentin and high-dose dexmedetomidine), PDB (placebo and low-dose dexmedetomidine), GDB (gabapentin and low-dose dexmedetomidine), and PDA (placebo and high-dose dexmedetomidine). Measurements were obtained at baseline (M0), 90 minutes after gabapentin or placebo administration (M1), and 15 minutes after dexmedetomidine administration (M2). Data are presented as mean ± standard deviation or median (maximum;minimum).

		Group			
Variable	**Moment**	**GD5**	**PD2**	**GD2**	**PD5**
ET	M0	152,692 ± 23,507^{Aa}	165 (145;215)^{Aa}	163,077 ± 25,863^{Aab}	152,692 ± 27,281^{Aab}
	M1	171,923 ± 13,775^{Aa}	155 (135;210)^{Aa}	157,917 ± 19,242^{Aa}	160 (90;180)^{Aa}
	M2	214,583 ± 34,605^{Ab}	209,231 ± 34,752^{Ab}	198,846 ± 44,260^{Ab}	193,462 ± 35,904^{Ab}
AT	M0	62,692 ± 13,481^{Aa}	60,769 ± 8,126^{Aa}	64,231 ± 10,576^{Aa}	55,385 ± 7,206^{Aa}
	M1	62,692 ± 12,848^{Aa}	59,231 ± 11,699^{Aa}	68,750 ± 21,011^{Aa}	57,181 ± 14,225^{Aa}
	M2	56 ± 5,164^{Aa}	69,615 ± 12,823^{Aa}	63,462 ± 13,379^{Aa}	57,917 ± 12,695^{Aa}
COp	M0	0,583 ± 0,170^{Aa}	0,615 ± 0,230^{Aa}	0,492 ± 0,131^{Aa}	0,515 ± 0,141^{Aa}
	M1	0,646 ± 0,194^{Aa}	0,662 ± 0,257^{Aa}	0,555 ± 0,181^{Aa}	0,6 ± 0,191^{Aa}
	M2	0,454 ± 0,151^{Aa}	0,382 ± 0,140^{Ab}	0,417 ± 0,208^{Aa}	0,550 ± 0,162^{Aa}
HRp	M0	188,167 ± 35,698^{Aa}	195,385 ± 36,705^{Aa}	185,167 ± 39,196^{Aab}	202 ± 29,808^{Aa}
	M1	185,769 ± 27,332^{Aa}	184,077 ± 38,036^{Aab}	201,455 ± 32,522^{Aa}	205,333 ± 21,047^{Aa}
	M2	108 (86;230)^{Ab}	141 ± 42,610^{Ab}	146,250 ± 33,401^{Ab}	165,250 ± 44,597^{Aa}
PVp	M0	91,508 ± 14,443^{Aab}	94,007 ± 14,373^{Aab}	87,7 ± 16,99^{Aab}	93,969 ± 17,507^{Aa}
	M1	94,2 ± 17,535^{Aa}	101,531 ± 16,738^{Aa}	94,175 ± 12,297^{Aa}	94,283 ± 18,157^{Aa}
	M2	67,6 (56,8;103,9)^{Ab}	79,423 ± 22,225^{Ab}	60,9 (45,9;125,2)^{Ab}	79,292 ± 17,897^{Aa}
VTIp	M0	9,304 ± 2,781^{Aa}	9,687 ± 2,476^{Aa}	8,806 ± 1,795^{Aa}	8,608 ± 1,686^{Aa}
	M1	8,54 (6,78;11,2)^{Aa}	11,7 (6,78;11,2)^{Aa}	8,525 ± 2,157^{Aa}	8,2 ± 1,962^{Aa}
	M2	8,549 ± 2,05^{Aa}	8,92 ± 1,523^{Aa}	7,958 ± 2,517^{Aa}	8,649 ± 1,077^{Aa}
PVAo	M0	88,738 ± 12,553^{Aa}	96,623 ± 16,288^{Aa}	90,062 ± 13,099^{Aa}	88,208 ± 14,990^{Aa}
	M1	87,275 ± 8,606^{Aa}	95,423 ± 14,431^{Aa}	88,558 ± 19,351^{Aab}	94,392 ± 22,664^{Aa}
	M2	68,4 (54,3;87,6)^{Aa}	81,667 ± 19,033^{Aa}	67,755 ± 16,442^{Ab}	81,8 ± 18,206^{Aa}
COAo	M0	0,5 (0,4;1,4)^{Aa}	0,654 ± 0,25^{Aa}	0,6 (0,3;0,7)^{Aa}	0,538 ± 32,844^{Aa}
	M1	0,646 ± 0,211^{Aa}	0,557 ± 0,205^{Aa}	0,583 ± 0,237^{Aa}	0,623 ± 0,205^{Aa}
	M2	0,4 (0,3;1,1)^{Aa}	0,545 ± 0,127^{Aa}	0,469 ± 0,18^{Aa}	0,562 ± 0,229^{Aa}
HRAo	M0	185,250 ± 32,844^{Aa}	192,769 ± 32,262^{Aa}	197,231 ± 28,601^{Aa}	196,154 ± 25,159^{Aab}

	M1	187,154 ± 24,474^{Aa}	197,615 ± 39,761^{Aa}	208 ± 25,902^{Aa}	201,538 ± 24,009^{Aa}
	M2	124,231 ± 36,111^{Ab}	146,538 ± 47,006^{Ab}	144,615 ± 28,579^{Ab}	160,846 ± 36,556^{Ab}
VTIAo	M0	8,717 ± 1,686^{Aa}	9,307 ± 3,325^{Aa}	8,089 ± 1,835^{Aa}	8,132 ± 1,766^{Aa}
	M1	8,278 ± 1,659^{Aa}	8,388 ± 2,536^{Aa}	7,277 ± 1,976^{Aa}	7,57 (5,96;10,2)^{Aa}
	M2	8,33 (7,2;14,3)^{Aa}	8,445 ± 2,028^{Aa}	7,772 ± 2,218^{Aa}	8,624 ± 2,143^{Aa}
IVRT	M0	40 (35;55)^{Aa}	40 (25;45)^{Aa}	40 (35;45)^{Aab}	35 (30;50)^{Aa}
	M1	42,917 ± 8,649^{Aa}	39,692 ± 4,837^{Aa}	36,364 ± 5,045^{Aa}	38,077 ± 5,604^{Aa}
	M2	47,692 ± 8,066^{Aa}	45 (40;55)^{Aa}	48,462 ± 9,658^{Ab}	40 (35;50)^{Aa}
E wave	M0	74,158 ± 11,027^{Aa}	90,623 ± 18,642^{Aa}	72,60 (65,1;118,5)^{Aa}	78,969 ± 11,911^{Aa}
	M1	73,646 ± 12,878^{Aa}	71,8 (65,1;114,4)^{Aa}	77,492 ± 11,445^{Aa}	78,969 ± 15,05^{Aa}
	M2	70,931 ± 13,926^{Aa}	81,831 ± 15,478^{Aa}	76,454 ±14,357^{Aa}	76,023 ± 12,934^{Aa}
E wave des	M0	67,083 ± 7,217^{Aa}	61,923 ± 13, 925^{Aa}	61,538 ± 13,131^{Aa}	60 (45;105)^{Aa}
	M1	70 (55;95)^{Aa}	62,769 ± 18,065^{Aa}	60 (45;80)^{Aa}	59,231 ± 15,117^{Aa}
	M2	62,692 ± 12,352^{Aa}	68,846 ± 13,564^{Aa}	60 (45,113)^{Aa}	67,308 ±14,806^{Aa}
A Wave	M0	53,450 (43,4;93,9)^{Aa}	68,038 ± 18,038^{Aa}	57,058 ± 7,369^{Aa}	59,846 ± 7,369^{Aa}
	M1	58,262 ± 12,005^{Aa}	59,3 (48,4;106,4)^{Aa}	58,567 ± 12,767^{Aa}	59,4 ± 12,808^{Aa}
	M2	47,108 ± 14,877^{Aa}	46,7 (35,9;95,2)^{Ab}	49,623 ± 13,875^{Aa}	52,6 (42,6;76)^{Aa}
E/A ratio	M0	1,307 ±0,198^{Aa}	1,280 (1,121;2,02)^{Aa}	1,385 ± 0,252^{Aa}	1,26 (4,56;9,99)^{Aa}
	M1	1,314 ± 0,352^{Aa}	1,231 ± 0,183^{Aa}	1,265 (1,12;2,61)^{Aa}	1,349 ± 0,193^{Aa}
	M2	1,652 ± 0,626^{Aa}	1,638 ±0,515^{Aa}	1,594 ± 0,307^{Aa}	1,478 ± 0,304^{Aa}

AT, pulmonary acceleration time; ET, ejection time, AT/ET ratio; COp, pulmonary cardiac output; HRp, pulmonary heart rate; VTIp, pulmonary velocity-time integral; PVp, pulmonary peak velocity (PVp); COAo,aortic cardiac output; HRAo, aortic heart rate; VTIAo, aortic velocity-time integral; PVAo, aortic peak velocity; E and A waves, transmitral flow; E/A, E'/A', LV free wall. E. wave in relation to LV free wall A' wave; IVRT, isovolumetric relaxation time. Capital letters (A and B) indicate statistical differences between groups within the same time point. Identical capital letters signify no significant difference ($p > 0.05$), while different capital letters denote a significant difference ($p < 0.05$). Lowercase letters (a and b) represent differences between time points within the same group. Identical lowercase letters indicate no significant difference ($p > 0.05$), while different lowercase letters indicate a significant difference ($p < 0.05$). Combination of lowercase letters (ab) indicates that the time point did not differ significantly from both previous and subsequent time points.

Table 4 – Echocardiographic functional parameters variables in healthy cats from different experimental groups. GDA (gabapentin and high-dose dexmedetomidine), PDB (placebo and low-dose dexmedetomidine), GDB (gabapentin and low-dose dexmedetomidine), and PDA (placebo and high-dose dexmedetomidine). Measurements were obtained at baseline (M0), 90 minutes after gabapentin or placebo administration (M1), and 15 minutes after dexmedetomidine administration (M2). Data are presented as mean ± standard deviation or median (maximum;minimum).

		Group			
Variable	**Moment**	**GD5**	**PD2**	**GD2**	**PD5**
LVSF	M0	52,527 ± 7,77^{Aa}	50,054 ± 11.327^{Aa}	58,723 ± 11,302^{Aa}	58,508 ± 12,791^{Aa}
	M1	52,438 ± 9,756^{Aa}	55,150 ± 12,924^{Aa}	60,225 ± 10,202^{Aa}	56,308 ± 12,921^{Aa}
	M2	44,269 ± 5,879^{Aa}	43,4 ± 8,788^{Aa}	46,227 ± 12,196^{Ab}	49,192 ± 6,459^{Aa}
LVEF	M0	85,909 ± 6,156^{Aa}	83 ± 10,847^{Aa}	93 (75;97)^{Aa}	88,917 ± 7,925^{Aa}
	M1	88 (61;96)^{Aa}	89,5 (63;97)^{Aa}	90,833 ± 6,235^{Aa}	92 (55;98)^{Aa}
	M2	78,846 ± 5,998^{Aa}	77,154 ± 9,406^{Aa}	79,364 ± 11,395^{Ab}	83,154 ± 5,829^{Aa}
IVS e'	M0	7,249 ±1,741^{Aa}	8,035 ± 1,512^{Aa}	8,343 ± 1,436^{Aa}	8,588 ± 1,658^{Aa}
	M1	7,71 (4,56;68,2)^{Aa}	8,410 ± 1,225^{Aa}	9,102 ± 1,356^{Aa}	8,391 ± 1,528^{Aa}
	M2	6,126 ± 1,265^{Aa}	7,19 (5,26;13,5)^{Aa}	7,43 ± 2,239^{Aa}	7,144 ± 1,001^{Aa}
IVS a'	M0	5,78 (4,21;10,9)^{Aa}	4,91 (4,44;8,06)^{Aa}	5,285 (4,2;11,7)^{Aa}	5,698 ± 1,321^{Aa}
	M1	5,892 ± 1,525^{Aa}	5,43 (4,38;7,89)^{Aa}	5,958 ± 0,438^{Aa}	6,001 ± 1,136^{Aa}
	M2	3,86 (2,28;8,24)^{Ab}	4,921 ± 1,121^{Aa}	4,678 ± 1,442^{Aa}	4,645 (4,03;7,71)^{Aa}
IVS s'	M0	7,088 ± 0,971^{Aa}	6,784 ±1,71^{Aa}	7,895 (5,08;8,94)^{Aa}	7,192 ±1,135^{Aab}
	M1	6,122 ± 0,994^{Aa}	6,532 ± 1,166^{Aa}	7,753 ± 1,547^{Aa}	7,966 ± 1,663^{Aa}
	M2	5,325 ±1,230^{Aa}	5,430 (4,21;7,01)^{Aa}	5,631 ± 1,785^{Aa}	5,681 ± 1,197^{Ab}
FW e'	M0	9,667 ± 1,925^{Aa}	8,965 ± 2,035^{Aa}	9,878 ± 1,654^{Aa}	10,045 ± 1,272^{Aa}
	M1	8,24 (7,54;11,2)^{Aa}	9,815 ± 1,593^{Aa}	9,485 ± 2,142^{Aa}	10,481 ± 2,050^{Aa}
	M2	9,096 ± 1,832^{Aa}	8,048 ±1,873^{Aa}	8,601 ± 2,832^{Aa}	9,065 ± 1,566^{Aa}
FW a'	M0	5,43 (3,86;13,3)^{Aa}	5,537 ± 1,03^{Aa}	5,43 (4,32;8,06)^{Aa}	5,782 ± 1,434^{Aa}
	M1	5,919 ± 1,534^{Aa}	5,731 ± 1,107^{Aa}	5,551 ± 1,131^{Aa}	6,260 ± 1,345^{Aa}
	M2	5,552 ± 1,938^{Aa}	5,502 ± 2,081^{Aa}	5,472 ± 1,532^{Aa}	5,083 ± 1,468^{Aa}
FW s'	M0	7,642 ± 1,448^{Aa}	6,66 (4,38;16,1)^{Aa}	6,92 ± 1,74^{Aa}	7,591 ± 1,556^{Aa}
	M1	6,837 ± 1,156^{Aab}	6,498 ± 1,039^{Aa}	7,006 ± 1,286^{Aa}	7,025 ± 1,849^{Aa}
	M2	5,284 ± 0,956^{Ab}	5,312 ± 0,984^{Aa}	5,651 ± 1,555^{Aa}	5,769 ± 1,587^{Aa}
TAPSE	M0	0,882 ± 0,104^{Aa}	0,864 ± 0,147^{Aa}	0,874 ± 0,177^{Aa}	0,833 ± 0,204^{Aa}
	M1	0,832 ± 0,156^{Aa}	0,879 ± 0,201^{Aa}	0,839 ± 0,197^{Aa}	0,879 ± 0,154^{Aa}
	M2	0,768 ± 0,169^{Aa}	0,865 ± 0,150^{Aa}	0,775 ± 0,132^{Aa}	0,888 ± 0,163^{Aa}
MAPSE	M0	0,573 ± 0,119^{Aa}	0,564 ± 0,160^{Aa}	0,5 (0,39;0,74)^{Aa}	0,635 ± 0,154^{Aa}
	M1	0,537 ± 0,101^{Aa}	0,556± 0,112^{Aa}	0,517 ± 0,145^{Aa}	0,586 ± 0,113^{Aa}
	M2	0,525 ± 0,125^{Aa}	0,508 ± 0,063^{Aa}	0,48 (0,39;0,65)^{Aa}	0,558 ± 0,118^{Aa}

LVSF, left ventricular shortening fraction; LVEF, left ventricular ejection fraction; E’, early diastolic myocardial velocity; A’, late diastolic myocardial velocity, S’ systolic myocardial velocity (S'); A'/E' ratio; FW, Free wall; IVS, Interventricular septum; TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion. Significant differences ($p < 0.05$). Capital letters (A and B) indicate statistical differences between groups within the same time point. Identical capital letters signify no significant difference ($p > 0.05$), while different capital letters denote a significant difference ($p < 0.05$). Lowercase letters (a and b) represent differences between time points within the same group. Identical lowercase letters indicate no significant difference ($p > 0.05$), while different lowercase letters indicate a significant difference ($p < 0.05$). Combination of lowercase letters (ab) indicates that the time point did not differ significantly from both previous and subsequent time points.

3.4 FIGURES

Figure 1 – Boxplot of Cat Stress Score (CSS) in healthy cats from different experimental groups (GD5, PD2, GD2, PD5) across evaluation moments (M0, M1, M2). GD5: gabapentin and high-dose dexmedetomidine; PD2: placebo and low-dose dexmedetomidine; GD2: gabapentin and low-dose dexmedetomidine; PD5: placebo and high-dose dexmedetomidine. CSS was assessed at baseline (M0), 90 minutes after gabapentin or placebo administration (M1), and 15 minutes after dexmedetomidine administration (M2). Boxes represent the interdecile range (10th to 90th percentiles), the horizontal line within the box indicates the median, and whiskers represent the minimum and maximum values. Asterisks (*) indicate statistically significant differences ($p < 0.05$).

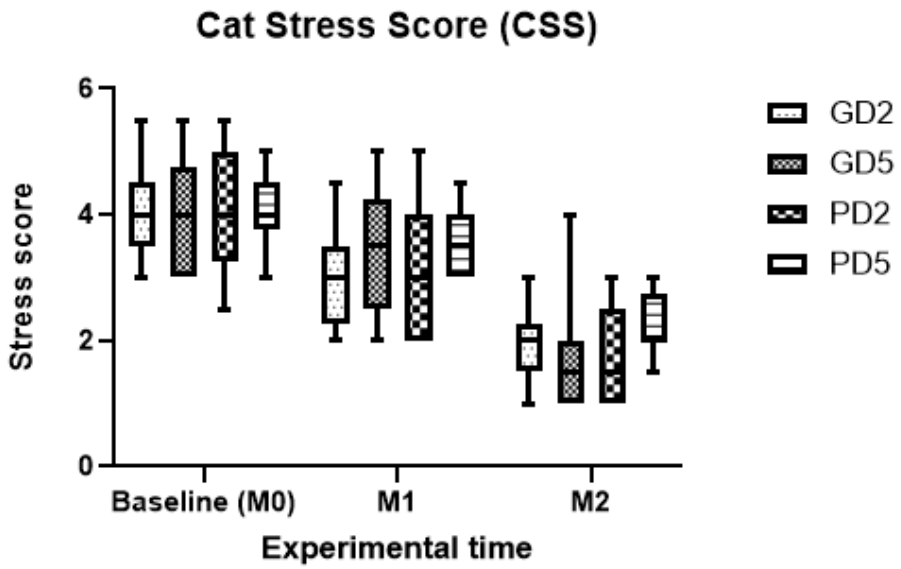
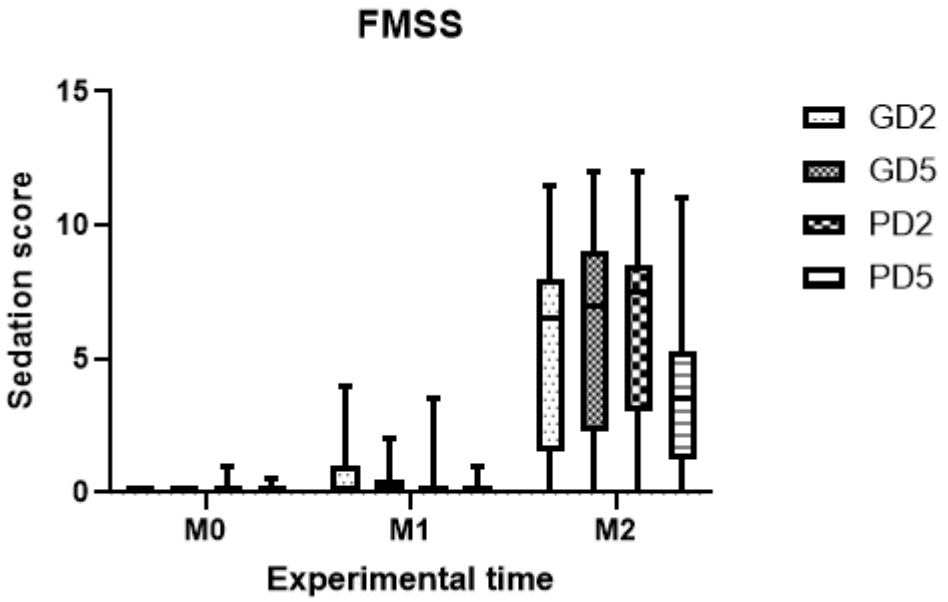


Figure 2 – Boxplot of Feline Multiparametric Sedation Score (FMSS) in healthy cats from different experimental groups (GD5, PD2, GD2, PD5) across evaluation moments (M0, M1, M2). GD5: gabapentin and high-dose dexmedetomidine; PD2: placebo and low-dose dexmedetomidine; GD2: gabapentin and low-dose dexmedetomidine; PD5: placebo and high-dose dexmedetomidine. CSS was assessed at baseline (M0), 90 minutes after gabapentin or placebo administration (M1), and 15 minutes after dexmedetomidine administration (M2). Boxes represent the interdecile range (10th to 90th percentiles), the horizontal line within the box indicates the median, and whiskers represent the minimum and maximum values. Asterisks (*) indicate statistically significant differences ($p < 0.05$).



4 CONSIDERAÇÕES FINAIS

A combinação de gabapentina e dexmedetomidina não promoveu um aumento significativo na sedação ou na redução do estresse em comparação com a dexmedetomidina isolada, conforme evidenciado pelos resultados semelhantes no CSS e FMSS entre os grupos. No entanto, o grupo GD5 apresentou uma redução mais acentuada da frequência cardíaca e uma maior incidência de regurgitação valvular cardíaca, sugerindo possíveis efeitos cardiovasculares.

Embora não tenham sido observadas alterações significativas na PAS e DC, a interação entre gabapentina e dexmedetomidina potencializou o efeito bradicárdico. Esses achados indicam que a gabapentina pode influenciar parâmetros cardiovasculares sem intensificar a sedação, ressaltando a necessidade de investigações adicionais sobre os mecanismos subjacentes a essas alterações e sua relevância clínica na anestesia veterinária.

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ANEXO A – Certificado de aprovação da CEUA/UFFS

UNIVERSIDADE FEDERAL DA FRONTEIRA SUL

Universidade Federal da Fronteira Sul

Comissão de Ética no Uso de Animais

CERTIFICADO

Certificamos que a proposta intitulada "EFEITOS SEDATIVOS E CARDIOVASCULARES DA DEXMEDETOMIDINA ISOLADA OU COMBINADA COM GABAPENTINA EM GATOS SAUDÁVEIS", protocolada sob o CEUA nº 1050090824 (ID 000692), sob a responsabilidade de **Tatiana Champion** *e equipe; Marina Marangoni; Luana de Melo Miguel* - que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino - está de acordo com os preceitos da Lei 11.794 de 8 de outubro de 2008, com o Decreto 6.899 de 15 de julho de 2009, bem como com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi **APROVADA** pela Comissão de Ética no Uso de Animais da Universidade Federal da Fronteira Sul (CEUA/UFFS) na reunião de 27/08/2024.

We certify that the proposal "Sedative and Cardiovascular Effects of Dexmedetomidine Alone or Combined with Gabapentin in Healthy Cats", utilizing 124 Cats (males or females), protocol number CEUA 1050090824 (ID 000692), under the responsibility of **Tatiana Champion** *and team; Marina Marangoni; Luana de Melo Miguel* - which involves the production, maintenance and/or use of animals belonging to the phylum Chordata, subphylum Vertebrata (except human beings), for scientific research purposes or teaching - is in accordance with Law 11.794 of October 8, 2008, Decree 6899 of July 15, 2009, as well as with the rules issued by the National Council for Control of Animal Experimentation (CONCEA), and was **APPROVED** by the Ethic Committee on Animal Use of the Federal University of South Border (CEUA/UFFS) in the meeting of 08/27/2024.

Finalidade da Proposta: Pesquisa (Acadêmica)

Vigência da Proposta: de 10/2024 a 03/2025 Área: Medicina Veterinária

Origem: Animais de proprietários
Espécie: Gatos sexo: Machos ou Fêmeas idade: 1 a 6 anos Quantidade: 124
Linhagem: Independe Peso: 2 a 6 kg

Realeza, 02 de setembro de 2024

Profa. Dra. Fabíola Dalmolin
Coordenadora da Comissão de Ética no Uso de Animais
Universidade Federal da Fronteira Sul

Biol. Cássio Batista Marcon
Vice-Coordenador da Comissão de Ética no Uso de Animais
Universidade Federal da Fronteira Sul

ANEXO B – Normas da revista Veterinary Anesthesia and Analgesia

Article structure

This section describes the article structure for this journal.

Sections

Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'.

Sections in the body of the manuscript (introduction to discussion) should not be separated by page breaks.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient detail to allow the work to be reproduced. Methods already published should be indicated by a reference: only relevant modifications should be described. Excessive recycling of words from previous manuscripts, including the methods section, will not be allowed. See Elsevier's Ethics in Research & Publication brochure.

Specify in Materials and methods the ethical review committee approval process and the international, national, and/or institutional guidelines followed. Provide evidence in Materials and methods that the principles of reduction, refinement, and replacement have been met.

Statistics

For help with statistical reporting please refer to the SAMPL Guidelines which are available on the Equator Network. Further useful information on best practices in reporting sample size calculations in Randomized Controlled Trials in the field of anaesthesia can be found in the following British Journal of Anaesthesia article: *'Pitfalls in reporting sample size calculation in randomized controlled trials published in leading anaesthesia journals: a systematic review'*.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section may be appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

- ***Title.*** Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. Ideally 12 words or fewer
- ***Author names and affiliations.*** Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled and in the correct order. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- ***Corresponding author.*** Clearly indicate who will handle correspondence at all stages of refereeing and publication, and which author will be the corresponding author post-publication. **Ensure that the e-mail address is given and that contact details are kept up to date by the pre-publication corresponding author.**
- ***Present/permanent address.*** If the first author who is not the corresponding post-publication author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. This information should be provided on the title page upon manuscript submission. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.
- **Acknowledgments (including sources of funding)**
- **Authors' contributions**
- **Conflict of interest statement**

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, references should not be included in the abstract. Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself. The abstract should be on a separate page and should not exceed 300 words. For original research articles and short communications, a structured abstract should be used with the following titles: Objective, Study design, Animals or Animal population, Methods, Results, Conclusions and clinical relevance. For review articles and "What is the Evidence?" articles the abstract should

be structured and usually should have the following headings: Objective, Databases used and Conclusions.

Keywords

Up to six keywords or phrases should be listed immediately after the abstract. Ideally, they should be MeSH headings.

Please use either British English or American English spelling (ensuring that this is consistent with the spelling used throughout the body of your manuscript) and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations

Define abbreviations at their first mention in the body of the manuscript (introduction through discussion). Ensure consistency of abbreviations throughout the article. A list of commonly used abbreviations is available here.

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, it is recommended to include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Math formulae

Please submit math equations as editable text and not as images. Present simple formulae in line with normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. Powers of e are often more conveniently denoted by exp. Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Footnotes

Footnotes should rarely be used. If used, indicate the position of the footnote in the text and present the footnote separately at the end of the article.

Artwork

This section describes the artwork for this journal.

Electronic artwork

General points

- Make sure you use uniform lettering and sizing of your original artwork.
- Preferred fonts: Arial (or Helvetica), Times New Roman (or Times), Symbol, Courier.
- Number the illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- For Word submissions only, you may still provide figures and their legends, and tables within a single file at the revision stage.
- Please note that individual figure files larger than 10 MB must be provided in separate source files.

Formats

Regardless of the application used, when your electronic artwork is finalized, please 'save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):

EPS (or PDF): Vector drawings. Embed the font or save the text as 'graphics'.

TIFF (or JPG): Color or grayscale photographs (halftones): always use a minimum of 600 dpi.

TIFF (or JPG): Bitmapped line drawings: use a minimum of 1000 dpi.

TIFF (or JPG): Combinations bitmapped line/half-tone (color or grayscale): a minimum of 600 dpi is required.

Please do not:

- Supply files that are optimized for screen use (e.g., PowerPoint, GIF, BMP, PICT, WPG); the resolution is too low.
- Supply files that are too low in resolution.
- Submit graphics that are disproportionately large for the content.

Color artwork

Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF), or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. **For color reproduction in print, you will receive information regarding the costs from Elsevier after receipt of your accepted article**. Please indicate your preference for color: in print or online only. Further information on the preparation of electronic artwork.

Figure captions

Ensure that each illustration has a caption. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used in the legend.

Tables

Please submit tables as editable text and not as images, Excel files, or embedded in Word files. Tables should be placed on separate page(s) at the end after the references list or in a separate file. Number tables consecutively in accordance with their appearance in the text. The caption should be placed above the table and explain the origin of the data and any table notes should be placed below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules.

References

This section describes the references for this journal.

Citation in text

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