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Sedation effect of midazolam, ketamine, and butorphanol on spectral Doppler ultrasound values in femoral and large abdominal arteries in cats

Efeito da sedação do midazolam, quetamina e butorfanol nos valores do ultrassom com Doppler espectral na artéria femoral e grandes artérias abdominais de gatos

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Abstract

Real time information about direction and type of blood flow can be obtained with Doppler ultrasound. In the literature it was not found data obtained with this method from celiac and cranial mesenteric artery in cats. Moreover, sedation of the animal is occasionally necessary to obtain more information on any blood vessel using this method. The purpose of this study was to evaluate the quantitative aspects of spectral waves formed from blood flow of the celiac, cranial mesenteric, renal, external iliac, femoral, and aortic arteries in healthy cats, and to compare them with the same animals when subjected to midazolam, ketamine, and butorphanol sedation. We also measured the heart rate. Twenty healthy adult cats were evaluated. The values obtained for resistivity index and pulsatility index from the celiac artery were 0.62 ± 0.10 and 1.29 ± 0.55, and those from the mesenteric artery were 0.68 ± 0.09 and 1.37 ± 0.39, respectively. Although heart rate was higher in sedated animals, no significant statistical difference was found in case of other parameters, except celiac artery end diastolic velocity and time averaged mean velocity and iliac artery resistivity and pulsatility index. Thus, we provide the Doppler velocimetry parameter from celiac and mesenteric arteries and conclude that this protocol does not alter the values of Doppler ultrasound in the selected vessels, except the celiac and iliac arteries.

Key words: Celiac artery. Cranial mesenteric artery. Renal artery. External iliac artery. Resistive index. Pulsatility index.

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Resumo

Informações em tempo real da direção e tipo de fluxo sanguíneo podem ser obtidas com ultrassonografia com Doppler. Existe na literatura dados relativos a esses parâmetros, em gatos não sedados, obtidos das artérias: aorta, renal, ilíaca e femoral; no entanto não foram encontrados na literatura dados relativos às artérias celíaca e mesentérica cranial. Além disso, ocasionalmente há necessidade de sedar animais inquietos ou agressivos, para que seja possível a realização deste exame. O objetivo do trabalho foi avaliar os aspectos quantitativos da onda espectral formada pelo fluxo sanguíneo das artérias: celíaca, mesentérica cranial, renal, ilíaca externa, femoral e aorta abdominal de gatos hígidos e compará-los aos obtidos dos mesmos animais submetidos à sedação com midazolam, cetamina e butorfanol. A frequência cardíaca também foi mensurada. Foram avaliados 20 gatos SRD adultos e saudáveis. Os valores encontrados em animais não sedados na artéria celíaca de índice de resistividade foi 0,62 ± 0,10 e índice de pulsatilidade 1,29 ± 0,55, enquanto da artéria mesentérica cranial, 0,68 ± 0,11 e 1,37 ± 0,39, respectivamente. Apesar da frequência cardíaca mais elevada nos animais sedados, não foram encontradas diferenças estatisticamente significativas dentre os demais parâmetros avaliados, exceto na velocidade diastólica final e velocidade média da artéria celíaca, e índice de resistividade e de pulsatilidade da artéria ilíaca. Dessa forma, foram fornecidos parâmetros dopplervelocimétricos da artéria celíaca e mesentérica cranial e conclui-se que o protocolo utilizado não alterou os valores encontrados por ultrassonografia Doppler nos vasos selecionados, exceto da artéria celíaca e da ilíaca.

Palavras-chave: Artéria celíaca. Artéria mesentérica. Artéria renal. Artéria ilíaca externa. Índice de resistividade. Índice de pulsatilidade.

Introduction

Doppler ultrasound provides non-invasive real-time information of the direction and type of blood flow (SZATMÁRI et al., 2001; CARVALHO; ADDAD, 2009).

Among the types of Doppler ultrasound, spectral Doppler allows graphical recording of qualitative and quantitative vascular information on changes in blood flow velocity at each cardiac cycle, in which, time is displayed on the horizontal axis, and the flow velocity on the vertical axis (CARVALHO et al., 2008).

To perform this exam, it is necessary to locate the vessel, adjust the sample volume, align the main flow vector such that it is parallel to the direction of blood flow, maintain the insonation angle below 60°, and subsequently acquire the graph with the spectral wave itself (CARVALHO; ADDAD, 2009), with no movement at the examination site. This procedure requires little time provided the animal cooperates. Thus, occasionally, sedation is needed to obtain the image (MINO et al., 2008), especially in restless, difficult to contain, or aggressive animals, since the movement of the arteries resulting from voluntary movement of the animal during the evaluation with Doppler, even when feasible, increases the examination time and difficulty (NOVELLAS et al., 2007).

Doppler velocimetry parameters can be used as a support in the diagnosis and prognosis of changes in the parenchyma of organs that are supplied by the evaluated vessels (VAN DER WOUDE; VANDERSCHUREN, 1999; CHANG et al., 2010). The celiac artery and cranial mesenteric artery supply mainly to the liver, spleen, stomach and small intestine, while the renal artery supplies to the kidney (CARVALHO et al., 2008; RIESEN et al., 2002); Thus, both neoplastic and inflammatory changes in organs can generate hemodynamic changes in these vessels, reflecting changes in the parameters obtained by spectral Doppler. In addition, it is known that acute thrombosis thrombi may not be visible by B-mode ultrasound, however, Doppler ultrasound may support the diagnosis and evaluate the degree of stenosis of the involved vessel in such cases (CARVALHO; TANNOUZ, 2009). As thrombus in cats usually affects the aorta at the iliac trifurcation (LAFORCADE, 2012), both external and femoral arteries can be evaluated to assess the level of vascular involvement in the hind limbs.

There are studies in the literature describing the Doppler velocimetric parameters of the celiac artery and cranial mesenteric artery found in healthy fasting and postprandial dogs (RIESEN et al., 2002; KIRSCHER et al., 2003; GASCHEN; KIRCHER, 2007), with disorders in organs supplied by these vessels (GASCHEN et al., 2005; GASCHEN; KIRCHER, 2007), including atopic dermatitis (BRUET et al., 2013) and acute normovolemic anemia (KOMA et al., 2005). However, no such data was found in the literature in cats.

The objective of this study was to describe the Doppler velocimetry values of celiac (CA), cranial mesenteric (MCA), left renal (LRA), left external iliac (LEIA), and left femoral artery (AF), abdominal aorta, caudal to renal artery (AOR) and cranial to external iliac (AOB), of healthy unsedated cats. Of these, the first two vessels do not have data published in the researched literature. The other objective of this study was to evaluate whether or not these parameters differed between non-sedated and sedated cats with midazolam, ketamine and butorphanol, in abdominal aorta, caudal to renal artery (AOR) and cranial to external iliac (AOT); celiac (CA), cranial mesenteric (MCA), left renal (LRA), left external iliac (LEIA) and left femoral artery (LFA).

Materials and Methods

The study population consisted of twenty female cats, between 8 months and 5 years old, weighing between 1.9 and 4 kg, healthy mixed breed, whose owners wanted to perform elective ovariohysterectomy. The cats were housed in the university for 24 hours before the experiment to perform tests that verified their sanity, which included clinical examination, blood test (blood count, ALT, FA, creatinine, urea, glucose, triglycerides, and cholesterol), urinalysis, abdominal ultrasound, electrocardiogram, and echocardiography. The animals were subjected to 12 h feeding restriction and 2h water restriction before vessel measurement. Trichotomy of the abdomen and medial surface of the left pelvic limb was performed on the day the animal was admitted.

Doppler ultrasound evaluation was done immediately before and 10 minutes after intramuscular application of midazolam 0.4 mg kg $^{-1}$ (generic drug, União Química, Brazil), 3 mg kg $^{-1}$ ketamine (Ketamina Fragra, Fragra Farmagrícola, Brazil) and 0.4 mg kg $^{-1}$ of butorphanol (Butormin, Holliday, Argentina). Duplex ultrasound examination was performed by an evaluator with a Mindray Z6 ultrasound device with a multifrequency linear transducer (7.5 to 10 MHz). After applying ultrasound gel to the skin, B-mode ultrasound was generated, with the animal in lateral decubitus, aiming at the location of the vessels, and when necessary, color Doppler was used. At least five similar spectral waves were recorded on the device for further analysis. Vessel data were collected in the following order: AOT, LEIA, AOR, LRA, LAF, CA and MCA. In the case of AOR, AOT, LRA, LEIA and LFA, longitudinal B-mode vessel images of at least three cardiac cycles were recorded for subsequent diameter measurement.

The velocimetric data obtained were: peak systolic velocity (PSV), final diastolic velocity (EnDV), time-avaraged mean velocity (TAMEAN), time-avaraged maximum velocity (TAMAX), resistivity index (RI) and pulsatility index (PI). RI was calculated by the equation (PSV-EnDV)/PSV, while PI was equal to (PSV-EnDV)/TAMAX (NOVELLAS et al., 2007).

The average of five consecutive waves of these data, as well as the three measurements of diameter at the time of systole were obtained. Heart rate was also assessed at vessel measurement times and their averages were calculated.

The owners signed an informed consent form and after the experiment, the animals were submitted for ovariohysterectomy. The study was approved by the University Animal Ethics Committee under protocol number 25552.

Statistical analysis was performed using the Microsoft Excel 2010 software, obtaining the mean ± standard deviation, and data comparison was obtained using the paired *t* test, considering the application of hypothesis tests with a significance level of 5%.

Results and Discussion

The spectral images obtained during the examination were further analyzed and the Doppler velocimetric values of CA, MCA, LRA, AOR, AOT, LEIA and LFA obtained are shown in Table 1.

Among the 20 animals used, CA and MCA evaluations were not possible in two of the non-sedated and four of the sedated ones.

During the examination in the sedated animals, 17 showed signs of excitement at the end of the examination, corresponding to 23 ± 5 minutes after protocol application, which allowed majority of the ultrasound examination, but promptly made us anesthetize for posterior ovariohysterectomy in 85% of the animals, not allowing prolongation of the examination or performing any other procedures. Excitation also prevented the evaluation of CA and MCA in three animals.

Biermann et al. (2012) reported that this protocol is an interesting combination for cats aiming at restraint for diagnostic procedures, as it generates acceptable sedation with minimal associated cardiovascular alteration. However, due to this excitement observed, depending on the situation and the complementary exams that motivate it, these drugs, at the doses used in the present study, may not be the most recommended, or perhaps require venous access with fluid therapy to the animal during sedation and previous preparation of another drug, such as propofol, to be used, if necessary.

The unviability of CA and MCA evaluation in the other animals (two non-sedated cats and one sedated) was due to the difficulty in positioning the sample volume at the vessel and the vessel wall interference in the spectral Doppler image formation, although the vessels were displayed in B mode.

The average heart rate rose from 178 ± 26 beats per minute (bpm) in non-sedated animals to 211 ± 41 bpm after sedation, showing a statistically significant difference ($p < 0.05$). Probably this increase was due to the use of ketamine, which exhibits increase in heart rate, cardiac output and blood pressure as side effects (AKKERDAAS et al., 2001). A previous study using the same animal species and drugs with equal doses found no statistical difference in heart rate before and after sedation; however, baseline values were higher than those found in the present study (213 ± 17 bpm). Management prior to the examination may have caused greater stress and could have been the cause of these higher baseline values found by Biermann et al. (2012), since they performed rectal temperature and blood pressure measurements before heart rate assessment.

No published data were found for the CA and MCA parameters obtained by Doppler ultrasound in cats. We obtained IR and IP values of 0.62 ± 0.10, 0.68 ± 0.11, 1.29 ± 0.55 and 1.37 ± 0.39, respectively.

Table 1. Values obtained with Doppler ultrasound of the celiac (CA), cranial mesenteric (MCA), left renal (LRA), left external iliac (LEIA), and left femoral (LFA) arteries, and abdominal aorta caudal to the left renal artery (OAR) and abdominal aorta close to the iliac trifurcation (OAT) of manually restrained, non-sedated cats and subsequently sedated with midazolam, ketamine, and butorfanol (mean ± standard deviation).

Vessel	Parameters	Non-sedated	Sedated	Significance
CA*	PSV (cm/s)	100.58 ± 29.80	87.53 ± 17.10	No (p=0.13317)
	EnDV (cm/s)	35.91 ± 11.25	27.61 ± 7.52	Yes (p=0.04202)
	TAMAX (cm/s)	55.17 ± 14.82	47.72 ± 13.14	No (p=0.06135)
	TAMEAN (cm/s)	34.71 ± 10.22	27.61 ± 7.52	Yes (p=0.01720)
	RI	0.62 ± 0.10	0.65 ± 0.07	No (p=0.29446)
	PI	1.29 ± 0.55	1.22 ± 0.25	No (p=0.67662)
MCA*	PSV (cm/s)	90.83 ± 30.17	88.95 ± 33.77	No (p=0.77725)
	EDV (cm/s)	30.04 ± 16.65	29.33 ± 16.16	No (p=0.68405)
	TAMAX (cm/s)	47.96 ± 20.97	48.82 ± 25.08	No (p=0.78861)
	TAMEAN (cm/s)	28.03 ± 10.81	29.33 ± 16.16	No (p=0.68405)
	RI	0.68 ± 0.11	0.66 ± 0.12	No (p=0.45849)
	PI	1.37 ± 0.39	1.33 ± 0.52	No (p=0.82902)
LRA	PSV (cm/s)	75.75 ± 11.78	73.38 ± 19.88	No (p=0.59001)
	EnDV (cm/s)	31.93 ± 9.49	31.73 ± 10.63	No (p=0.94303)
	TAMAX (cm/s)	46.70 ± 9.64	45.48 ± 13.30	No (p=0.67753)
	TAMEAN (cm/s)	26.55 ± 8.39	23.00 ± 9.81	No (p=0.13152)
	RI	0.58 ± 0.10	0.56 ± 0.08	No (p=0.67185)
	PI	0.94 ± 0.26	0.95 ± 0.30	No (p=0.91254)
	Diameter	0.13 ± 0.17	0.13 ± 0.19	No (p=0.81665)
LEIA	PSV (cm/s)	106.00 ± 28.36	97.05 ± 24.92	No (p= 0.07949)
	EnDV (cm/s)	17.93 ± 7.00	20.44 ± 9.29	No (p= 0.26089)
	TAMAX (cm/s)	35.59 ±9.80	36.35 ± 13.99	No (p= 0.78044)
	TAMEAN (cm/s)	20.75 ± 8.01	21.63 ± 9.40	No (p=0.66795)
	RI	0.84 ± 0.05	0.80 ± 0.07	Yes (p=0.01103)
	PI	2.41 ± 0.43	2.17 ± 0.57	Yes (p=0.01675)
	Diameter	0.18 ± 0.02	0.17 ± 0.02	No (p=0.33811)
LFA	PSV (cm/s)	81.67 ± 12.12	78.57 ± 15.80	No (p=0.40912)
	EnDV (cm/s)	14.54 ± 4.24	16.04 ± 9.23	No (p=0.49280)
	TAMAX (cm/s)	29.35 ± 6.34	28.58 ± 9.48	No (p=0.69406)
	TAMEAN (cm/s)	16.92 ± 3.95	16.59 ± 6.90	No (p=0.84695)
	RI	0.82 ± 0.06	0.81 ± 0.11	No (p=0.58602)
	PI	2.27 ± 0.56	2.29 ± 0.73	No (p=0.94849)
	Diameter	0.11 ± 0.02	0.11 ± 0.01	No (p=0.64633)

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ORA	PSV (cm/s)	120.81 ± 19.48	116.65 ± 19.27	No (p=0.31854)
	EnDV (cm/s)	26.80 ± 8.98	10.82 ±24.72	No (p=0.49498)
	TAMAX (cm/s)	50.17 ± 13.68	45.72 ± 12.83	No (p=0.16432)
	TAMEAN (cm/s)	32.42 ± 9.11	29.21 ± 9.10	No (p=0.16068)
	RI	0.78 ± 0.07	0.79 ± 0.09	No (p=0.62558)
	PI	1.86 ± 0.45	2.00 ± 0.55	No (p=0.31867)
	Diameter	0.30 ±0.02	0.30 ±0.02	No (p=0.79145)
AOT	PSV (cm/s)	113.85 ± 21.37	109.91 ± 20.82	No (p=0.38402)
	EnDV (cm/s)	25.66 ± 9.87	24.92 ± 7.78	No (p=0.73495)
	TAMAX (cm/s)	47.53 ± 12.52	43.24 ± 12.53	No (p=0.16001)
	TAMEAN (cm/s)	30.98 ± 10.44	26.60 ± 8.27	No (p=0.05467)
	RI	0.78 ± 0.06	0.77 ± 0.08	No (p=0.50610)
	PI	1.85 ± 0.41	1.98 ± 0.59	No (p=0.26860)
	Diameter	0.28 ± 0.02	0.27 ± 0.02	No (p=0.07729)

* The diameter was not measured. Only 14 animals allowed the examination of these vessels before and after, unlike the other vessels, which were measured in the 20 animals.
PSV = peak systolic velocity, EDV = final diastolic velocity, EnDV = initial retrograde diastolic velocity, TAMAX = time-averaged maximum velocity, TAMEAN = time-averaged mean velocity, RI = resistivity index and PI = pulsatility index. Significance level=5%.

No statistically significant difference was observed between non-sedated and sedated animals, except for CA and LEIA (Table 1). In the first case, a statistically significant reduction in TAMEAN and EnDV was observed. Although TAMEAN has a linear relationship with blood flow and thus can be a good predictor of hemodynamic changes where the sectional area of the vessel remains the same (KOMA et al., 2005); and since the final moment of diastole (EnDV) is the ideal period to assess vascular resistance (CARVALHO et al., 2008), these velocity changes did not induce changes in RI and/or PI, which are indices that serve as indicators of indirect peripheral vascular resistance (NOVELLAS et al., 2007; REIS et al., 2014). Interestingly, both RI and PI are more reliable data than direct velocity estimation by Doppler ultrasound, as they are not angle dependent, allowing small and tortuous vessels to be better evaluated (NOVELLAS et al., 2007). Thus, perhaps the cause for this statistically significant difference in the case of TAMEAN and EnDV was some problem in the proper placement of the insonation angle in CA, rather than the change in blood flow velocity itself.

In the analysis of the values obtained from the LEIA, a statistical difference was observed only in the RI and PI, where there was a reduction in the values in sedated animals. Although there was no statistically significant difference between PSV and EnDV, there was a tendency for PSV to decrease in this vessel, which certainly contributed to these findings. The occurrence of these changes, without any sign of RI and PI modification in LFA, may be related to reduced resistance in other branches of the LEIA. The only branch of the LEIA before the vascular gap (between the caudal margin of the aponeurosis of the external oblique abdomen muscle and the pelvis) is the deep thigh artery, which originates near it. After its passage through the vascular gap, the LEIA becomes the femoral artery and soon emits a branch called the lateral circumflex femoral artery, continuing as the femoral artery on the medial thigh (EVANS; DELAHUNTA, 2010), where the evaluations were performed.

Data regarding the abdominal aorta caudal to the renal artery, as well as the renal artery, in non-sedated Persian cats, have already been described by Carvalho et al. (2009), being described for caudal aorta to renal artery: diameter 0.38 ± 0.04 cm, PSV 53.17 ± 13.46 cm/s, EnDV 20.73 ± 7.17 cm/s; while of the left renal artery: diameter 0.15 ± 0.02 cm, PSV 40.96 ± 9.08 cm/s, EnDV 18.46 ± 5.34 cm/s and RI = 0.55 ± 0.07. As for the data from the left external iliac artery and left femoral artery, Jarreta et al. (2010) described as normal values for the first: diameter 0.23 ± 0.04, PSV 63.63 ± 22.46; and for the second: diameter 0.19 ± 0.02, PSV 65.93 ± 30.42, however it does not describe if any sedation was used. Reis et al. (2014) reported that they found the following in cats not sedated for the femoral artery: diameter 0.17 ± 0.03, PSV 34.54 ± 8.03cm/s, EnDV 10.19 ± 2.77 cm/s, IP 1.27 ± 0.48 and IR, 0.78 ± 0.28.

In other words, when comparing the data of non-sedated cats obtained in this study with that described by other authors, we observed higher mean values of the cited parameters of renal artery PSV and EnDV and femoral artery PSV, EnDV and PI, however, smaller diameters in LEIA and LFA were observed. The difference between these values may be related to breed, animal size, methodology employed, animal management and sample volume and equipment used. We used mixed breed, while Carvalho et al. (2009) used Persian cats, which usually tend to be a calm breed, whereas Jarreta et al. (2010) and Reis et al. (2014) used several breeds. The size of the animals may consequently affect the diameter of the vessel, being used in this case only cats between 1.9 and 4 kg. The methodology and management applied can also affect the data obtained, considering that we leave the animals hospitalized for 24 hours, which may impose increased stress on them. In addition, Reis et al. (2014) emphasized in their work the use of the insonation angle set at 25°, and with this, there was a greater challenge to adjust the sample volume, which created a limitation when determining the maximum velocities of femoral arterial blood flow and this would justify the lower values found, when compared to previous works (REIS et al., 2014), as in this one.

Conclusions

We defined normal parameters for CA and MCA, and concluded that the protocol used did not change the values found by Doppler ultrasound in the selected vessels, except for the celiac and external iliac artery, in cats. Thus, when evaluating a restless or aggressive feline patient to find out if there is vascular hemodynamic disturbance, this protocol offers a viable alternative.

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