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Evaluation of Muscle Blood Flow in Dogs with Chronic Degenerative Mitral Valve Disease under Treatment

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ABSTRACT

In humans with clinically established heart failure, it has been widely suggested that many symptoms are attributable to peripheral perfusion abnormalities located, above all, in the skeletal muscle and not to central cardiac haemodynamic measurements. In veterinary patients, little is known about the real associated of muscle blood flow alterations in different clinical disorders. In dogs, the most common cause of heart failure is Chronic Degenerative Mitral Valve Disease (CDMVD). Thus, the aim of this work was to compare different quantitative measures related to peripheral muscular blood flow in healthy dogs and in dogs with advanced CDMVD under treatment. For this, the transcutaneous Doppler ultrasound, that is a non-invasive quantitative method to evaluate blood flow changes, was used. The data were obtained from femoral artery of seven healthy dogs and seven dogs with CDMVD that were receiving cardiovascular treatment at home. The results demonstrated that the resistance parameters of the femoral blood flow were significantly higher in dogs with CDMVD, compared with those of healthy dogs. The mean values of the femoral blood volume were lower in dogs with CDMVD in relation to healthy dogs. In conclusion, this study suggests that despite the cardiac therapy, the dogs may have variations in muscle blood flow that could contribute to the progression of heart disease and impair peripheral perfusion.

Key words: Heart failure, canine, therapy, vascular, doppler

INTRODUCTION

Chronic mitral valve endocardiosis, also known as chronic degenerative mitral valve disease, is the most common cause of Heart Failure (HF) in dogs and is responsible for the majority of all heart problems in this species (Ware, 2014). The CDMVD is caused by a thickening and shortening of the valves, sometimes accompanied by nodules on the valve leaflets (Ware, 2014; Madron, 2015). Currently, one of the principal methods of investigating CDMVD is Doppler echocardiography. This exam is a non-invasive method of diagnosing morphological, functional and haemodynamic changes capable of determining the etiology of different heart problems (Madron, 2015). Severe cases of mitral regurgitation may present a regurgitant valve that corresponds to a high proportion of the total volume of blood ejected by the left ventricle, which can severely impair cardiac output and lead to signs of HF (Ware, 2014; Madron, 2015). In humans with clinically established HF, it has been widely suggested that many symptoms are attributable to peripheral functional abnormalities located mainly in the skeletal muscle and not to central cardiac haemodynamic measurements, obtained by echocardiography (Franciosa *et al*., 1981; Mancini *et al*., 1986; Wilson *et al*., 1993;

Wilson *et al*., 1995). The traditional view is that abnormalities in peripheral circulation in patients with HF are the result of major neurohormonal activation and the consequent reduction in tissue blood perfusion, whether during exercise or at rest (Ware, 2014). A recent study in dogs with different congenital or acquired heart diseases showed that animals with moderate or severe HF have a significantly reduced muscle blood flow volume, compared with healthy animals (Nogueira *et al*., 2011). However, this study did not involve a critical evaluation of each specific heart disease (e.g. CDMVD), or of the effects of classical cardiac therapy on muscular peripheral blood perfusion.

Transcutaneous Doppler ultrasound is a non-invasive quantitative method that gives a better understanding of the haemodynamics in large and small surface arteries, enabling morphological changes and muscle blood flow velocity in the surface arteries to be evaluated (Szatmari *et al*., 2001). Bearing in mind that some information on arterial resistance cannot be obtained based on absolute blood flow velocities, some peripheral Doppler indices have been developed. These indices are calculated based on the ratios between blood flow velocities in a particular vessel (Szatmari *et al*., 2001). The pulsatility index (Szatmari *et al*., 2001) and the ratio of peak reverse velocity to peak systolic velocity (Arbeille *et al*., 1995), obtained by the Doppler spectrum for peripheral flow relate, as has been demonstrated, to the resistance of the blood in an artery (Arbeille *et al*., 1995; Szatmari *et al*., 2001). Given that the femoral artery is the main vessel responsible for blood perfusion of the largest body muscle area (posterior limb), the influences on blood flow, arising from mitral regurgitation secondary to CDMVD, can lead to changes in muscle haemodynamics that have not yet been fully clarified. This evidence may suggest additional clinical aspects for our understanding of intolerance to exercise and pathophysiology of HF in patients with CDMVD. The information from peripheral blood flow of a large muscle area may also be relevant for an evaluation of the influence of cardiac therapy on peripheral perfusion in patients with CDMVD. This work, therefore, seeks to compare different quantitative measurements related to peripheral blood flow of the femoral artery in healthy dogs and in dogs with advanced CDMVD receiving medication therapy to determine whether the therapy is capable of maintaining adequate muscle tissue perfusion in these patients.

MATERIALS AND METHODS

Animals: The data were obtained from seven healthy dogs and seven dogs with CDMVD, coming from the department of clinical care of a veterinary teaching hospital. The dogs with CDMVD presented at least one episode of clinical HF and that were receiving cardiovascular therapy at home (e.g. furosemide, spironolactone, benazepril, omega 3), according to the recommendations of Atkins *et al*. (2009). None of the animals received pimobendan. All the animals underwent a physical, radiographic, electrocardiographic and echocardiographic evaluation. The animals were divided into:

- **Group I:** Healthy dogs that received no treatment (Class A, according to Atkins *et al*. (2009))
- **Group II:** Dogs with CDMVD receiving cardiovascular therapy (Class C, according to Atkins *et al*. (2009))

Heart rate: The Heart Rate (HR) was obtained by synchronic electrocardiography at the time of carrying out the Doppler ultrasound exam of the femoral artery. Dogs with pathological cardiac arrhythmias were excluded from the experiment.

Blood pressure: The Systolic Arterial Pressure (SAP) was obtained for all the dogs by the Doppler method, according to the guidelines of Brown *et al.* (2007).

Echocardiography: The echocardiographic exam was carried out in all the animals, without any kind of sedation or anaesthesia, using the bidimensional, M-mode, Pulsed Wave (PW), Continuous Wave (CW), Colour Flow Mapping (CFM) and Tissue Doppler Imaging (TDI) methods. An echocardiography Doppler device (MyLab 40, Esaote®) was used, with electronic sector scan transducers of 3-11 MHz and electrocardiographic monitoring. The electrodes were placed on the distal part of the fore legs and hind legs (Madron, 2015). All the exams were recorded for subsequent evaluations.

In the bidimensional mode the heart chambers were evaluated and especially in the right transversal parasternal view, the diameter of the Left Atrium (LA) and the dimension of the root of the aorta (AO) were measured. In the Doppler colour flow mapping mode, in the left apical four-chamber parasternal view, the presence of Mitral Regurgitant Flow (MRF) to the left atrium was evaluated (Madron, 2015). Also in the same view, the mitral flow waves (E and A waves) and the Isovolumetric Relaxation Time (IVRT) were observed and in the tissue Doppler imaging mode, the Em, Am and S waves of the septal segments of the left ventricle were measured (Chetboul, 2015). Three consecutive measurements were taken for each variable and the mean value was calculated. Based on the mean values, the following relations were established, within the echocardiographic variables previously evaluated: LA/AO, E/A and E/Em.

Doppler ultrasound exam of the femoral artery: All the haemodynamic measurements were performed using a bidirectional pulsed Doppler device (MyLab 40, Esaote®). An electronic transducer with imaging frequency of 5-10 Mhz was used for the recording. The Doppler spectrum was obtained for the first portion (1-2 cm distal from the point of origin) of the right common femoral artery. The fur was shaved from the region to be evaluated. The lumen of the common femoral artery was observed as a sonolucent area, in the areas where the echogenicity was increased due to the arterial wall. Coloured Doppler was used to confirm the presence of blood flow and the arterial dimension. The region with the greatest diameter was measured with the ultrasound bundle longitudinal to the main axis of the vessel. The volume of the sample was placed in the same site, positioned in the centre of the vessel. An angle of 25° between the lumen of the artery and the ultrasound bundle was used to obtain the pulsed Doppler spectrum in all the animals. The parameters recorded were: Peak Systolic Velocity (PSV), Peak Early Diastolic Velocity (PEDV) and Peak Late Diastolic Velocity (PLDV), Mean Velocity (MV), Velocity-Time Integral (VTI), Pulsatility Index (PI), Femoral Flow Volume (FFV) and Femoral Artery Diameter (FAD). The FFV was calculated by the formula: FFV = FA×VTI, where FA is the area of the femoral artery ($FA = \pi(FAD/2)^2$. The Acceleration Index (AI) and Deceleration Index (DI) of the PSV were also evaluated. The AI was calculated based on the ratio between the PSV and its acceleration time and the DI was calculated based on the ratio between the PSV and its deceleration time. Three consecutive measures were performed for each variable and the means were calculated. Based on the mean values, the ratio between PEDV and PSV was also studied.

Statistical analysis: The statistical analysis was carried out using the software SPSS 17.0, Microsoft Windows. The normality of distribution of the results was evaluated by the Shapiro-Wilk

method. For the variables with normal distribution, their means were compared by the t-test and for those without normal distribution, their means were compared by the Mann-Whitney test. A value of $p<0.05$ was used to define statistical significance.

RESULTS

Among the healthy dogs (Group I), there were seven animals with a mean weight of 6.62±3.86 kg and with a mean age of 113.14±24.84 months. Of the dogs in the CDMVD group (Group II), there were seven animals with a mean weight of 6.96±3.01 kg and with a mean age of 130.28±29.74 months. The breeds included in both groups are listed in Table 1. The animals of group II presented clinically controlled HF at the time of the study. On radiographic examination, left atrial enlargement was observed, without evidence of pulmonary oedema. In all the animals of group II, the echocardiographic exam showed severely thickened mitral valves and the presence of mitral regurgitation, with an increase in the left atrium confirmed by the LA/AO ratio (Table 2). No significant differences were found in the comparison of weight ($p = 0.535$) or age ($p = 0.724$) between the two groups. A characteristic sinusal heart rate was found in all the animals of both groups. The HR and SAP values did not show any statistical difference between the two groups (Table 2). In all the dogs of the two groups, the blood flow pattern in the femoral artery was triphasic, with predominant PSV, followed by a single antegrade wave (PEDV) and a late retrograde wave (PLDV). The Doppler spectrum diagram of blood flow in the femoral artery was laminar in both groups.

Table 1: Distribution of breeds in group I and group II

Breeds	Group I	Group II	Total
Miniature poodle	5	3	8
Daschund	1	2	3
Yorkshire terrier	1	2	3
Total	7	7	14

Table 2: Values for heart rate and blood pressure, as well as for the echocardiographic parameters and those obtained by doppler ultrasound of the right common femoral artery [Mean±DP (min-max limits)] of group I and group II

Haemodynamic variables	Group I	Group II	Significance
HR (beats/min)	107.71±36.49 (64-172)	118.14±27.75 (74-155)	No $p = 0.623$
SAP (mm Hg)	124.13±12.03 (109.30-152.26)	137.00±14.77 (107.33-153.00)	No $p = 0.714$
LA/AO	1.28±0.16 (1.00-1.50)	2.39±0.56 (1.70-3.10)	Yes $p = 0.001$
E/IVRT	0.011±0.003 (0,01-0,02)	0.018±0.009 (0.01-0.03)	Yes $p < 0.001$
E/A	1.15±0.25 (0.80-1.63)	1.68±0.58 (0.72-2.43)	Yes $p = 0.028$
Em (m s^{-1})	0.07±0.02 (0.04-0.11)	0.10±0.35 (0.05-0.14)	No $p = 0.166$
Am (m s^{-1})	0.07±0.03 (0.04-0.15)	0.11±0.04 (0.08- 0.18)	No $p = 0.513$
Sm (mL min^{-1})	0.09±0. 031 (0.05-0.14)	0.10±0. 011 (0.08- 0.11)	Yes $p = 0.038$
FAD (cm)	0.19±0.06 (0.13-0.32)	0.25±0.04 (0.20-0.33)	No $p = 0.558$
VTI (cm)	3.06±1.03 (2.00-4.40)	2.11±1.14 (1.06-4.50)	No $p = 0.594$
MV (cm s^{-1})	10.17±2.50 (7.30-14.70)	7.30±2.60 (3.90-10.60)	No $p = 0.845$
PSV (cm s^{-1})	50.63±12.55 (32.20-71.50)	51.75±16.47 (27.20-75.50)	No $p = 0.426$
PEDV (cm s^{-1})	6.51±3.62 (3.80-11.90)	9.59±4.14 (4.60-15.50)	No $p = 0.567$
PLDV (cm s^{-1})	7.54±3.04 (4.40-12.40)	9.09±3.29 (3.70-13.00)	No $p = 0.726$
AI	29.84±9.60 (19.00-49.00)	30.57±5.43 (22.00-35.00)	No $p = 0.174$
DI	0.64±0.20 (0.33-0.99)	1.04±0.59 (0.28-1.95)	Yes $p = 0.038$
FFV (mL min^{-1})	13.08±14.75 (3.04-36.05)	12.19±7.90 (3.51-26.80)	Yes $p = 0.005$
PEDV/PSV	0.12±0.04 (0.08-0.19)	0.18±0.04 (0.13- 0.25)	Yes $p = 0.035$
PI	5.90±0.89 (4.29-6.89)	9.54±5.30 (4.59-20.40)	Yes $p = 0.001$

HR: Heart rate, SAP: Systolic arterial blood pressure, LA/AO: Relation between left atrium and aorta, E/IVRT: Relation between peak velocity of early diastolic transmitral flow and isovolumic relaxation time, E/A: Relation between peak velocity of early diastolic transmitral and peak velocity of late diastolic transmitral, Em: Peak velocity of early diastolic mitral annular motion of the mitral annulus, Am: Peak velocity of late diastolic mitral annular motion of the mitral annulus, Sm: Peak velocity of systolic mitral annular motion of the mitral annulus, FAD: Femoral artery diameter; FVI: Flow velocity integral, MV: Blood mean velocity, PSV: Peak systolic velocity, PEDV: Peak early diastolic velocity, PLDV: Peak late diastolic velocity, AI: Acceleration index, DI: Deceleration index, FFV: Femoral flow volume, IP: Pulsatility index, Group I: Healthy dogs, Group II: Dogs with CDMVD, CDMVD: Chronic degeneration mitral valve disease

The mean values for heart rate, arterial pressure, as well as the echocardiographic parameters and those obtained for the duplex Doppler ultrasound of the right common femoral artery in both groups and their respective statistical significances, are shown in Table 2. This table shows that in the analysis of echocardiographic variables, it was possible to see a statistical difference between the groups studied for the E and Sm waves. Both the E wave and the Sm wave were significantly greater in the animals of group II, compared with the animals of group I. Of the ratios between the echocardiographic variables, a significant statistical different was observed between LA/AO, E/A and E/IVRT in the comparison between the groups. The LA/AO and E/IVRT ratios were significantly higher in the animals of group II than in those of group I.

In the statistical studies of the variables for femoral artery blood flow, it was apparent that the PI, DI and PEDV/PSV ratio had significant statistical difference between the groups studied. The PI, DI and PEDV/PSV ratio were significantly higher in the animals of group II, compared with those of group I. It should be emphasized that although the other variables did not demonstrate any significant difference between the groups studied it was seen that the mean MV and FFV values were lower in group II, compared with group I. Another variable worth emphasizing, in view of the mean measurements of its results, is the PEDV, which was higher in the animals of group II than in those of group I.

DISCUSSION

The variables obtained in the echocardiographic exam were indicative of the presence of alterations compatible with CDMVD. The LA/AO ratio was significantly increased in the animals of group II, compared with those of group I. These findings are also indicative of the presence of advanced CDMVD (Madron, 2015). In addition, the statistical differences observed in some central haemodynamic indices, like the E/A and E/IVRT ratios, showed the presence of HF in group II (Schober *et al*., 2010). Thus, the comparison between the groups with and without CDMVD, accompanied by the presence of HF, was clearly differentiated from an echocardiographic point of view, based on the description of Schober *et al*. (2010).

One of the main conclusions of this study was that animals with CDMVD presented major modifications in muscle perfusion compared with the healthy animals, despite the cardiovascular therapy administered. Of the variables that presented a significant difference between the two groups, DI and FFV, PEDV/PSV ratio and PI are highlighted. The variables for DI (Fronek *et al*., 1976) and PEDV/PSV ratio (Arbeille *et al*., 1995) have traditionally been described as indicators that are sensitive to peripheral resistance. In the present study, the two variables were increased in group II in relation to group I. These results are in accordance with the literature (Mitchell *et al*., 2001), bearing in mind that in patients with HF, various neurohormonal mechanisms are activated, which increase peripheral resistance, in an attempt to improve the cardiac output and maintain peripheral blood flow (Ware, 2014; Madron, 2015). Another variable that demonstrated sensitivity to the increase in this resistance was PI, which was higher in group II than in group I. The increase in this index also reflects a high peripheral resistance (Mitchell *et al*., 2001), which, as already mentioned, would be expected in patients with HF. However, it should be highlighted that the increase in resistance was not detected in the calculation of SAP, which remained within the normal limits and showed no significant difference between the groups. Meanwhile, in the present study, the Doppler evaluation of femoral artery blood flow showed a significant decrease in FFV between the two groups evaluated. This was an important finding in this study in dogs, as it suggests that although the arterial pressures were

normal, the animals showed impairment of muscle blood perfusion in group II, compared with group I. These results also suggest that despite the cardiovascular therapy instituted in group II, as recommended in the literature (Atkins *et al*., 2009), this therapy was not sufficient to establish peripheral muscular perfusion comparable to that of the animals without HF. A study carried out in Denmark reported the effects of CDMVD, in various degrees of severity, on peripheral arterial pulse wave variation (Tarnow *et al*., 2004). That study concluded that the reduction in blood pulse of the femoral artery was due to a regional or local reduction in blood flow as a result of the CDMVD (Tarnow *et al*., 2004). As demonstrated in studies with humans, the reduction of muscular blood flow is considered, by some authors, to be an essential mechanism in the onset of exercise intolerance in HF (Richardson *et al*., 2003). Thus, larger diagnostic and therapeutic studies on the peripheral circulation need to be performed in dogs, seeking to improve blood perfusion to the muscle tissues in these patients with HF due to CDMVD.

One of the limitations that can be considered in the present study is that the evaluation of peripheral blood flow in both groups was restricted to the femoral artery. Thus, we do not know whether similar alterations are present in other vessels of the greater arterial network. Neither do we know, whether the differences found in femoral arterial flow would be similar in the proximal aorta, or in other peripheral arteries of the same animal with HF due to CDMVD. However, alterations in resistance to blood flow, reflected in the proximal aorta, may be capable of altering the blood flow impedance of the left ventricle, increasing left ventricular systolic stress and impairing the opening of the aortic valve. This is a relevant aspect, particularly in patients with CDMVD, as the increase in this vascular impedance could worsen mitral regurgitation during the left ventricular systole.

In conclusion, this study suggests that despite the cardiac therapy, the dogs with CDMVD may have variations in muscle blood flow that could contribute to the progression of heart disease and impair peripheral perfusion. However, this topic requires further detailed studies in veterinary medicine.

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