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Postgraduate School of Veterinary Science

**Pathogenesis and diagnostics of cardiopathies of dogs
and ferrets in the light of echocardiography**

Ph.D.Thesis

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Introduction

My studies were based on echocardiography, which is an essential method in any case of suspected heart disease in the modern human and veterinary diagnostics as well.

In the first part of the study we described a long term (three months) echocardiographic follow-up of cardiac dilation due to an experimentally induced chronic volume overload in dogs. We have not found similar data in the literature by using this method.

In the second part of the study we have confirmed, that the measurement points for the diameter of the left atrium just above the mitral annulus also can be used in dogs suffering from cardiac disease showing atrial dilation. This technique was established for healthy dogs in a previous study at our institution and we have successfully applied it for cardiac patients.

The third aim of my study was to describe the ECG and echocardiographic parameters of healthy, conscious ferrets as we did not find any data in the literature, as previous studies were performed on sedated animals. In this work we have determined ECG and echocardiographic reference values for healthy ferrets which can be of international interest.

Echocardiographic characterization of volume overload induced cardiac dilatation in a canine experimental model

From etiological and pathophysiological point of view, chronic heart failure is not a uniform entity. However, in most conditions the final pathway is a progressive cardiac dilatation leading to intractable stage of heart disease. The aim of this study was to characterize the pathological changes in cardiac morphological and functional variables induced by chronic volume overload applying serial echocardiographic studies during a 12-week period. Another objective of our work was to determine whether two-dimensional (2DE) and M-mode

echocardiography, used as routine diagnostic procedures in veterinary clinical medicine, provide accurate data on the development of morphological cardiac changes.

Twelve 1 to 1.5-year-old Beagle dogs (6 males and 6 females) of 5 to 10 kg body weight were used in the study. Bilateral arteriovenous fistulas were created between the common femoral arteries and femoral veins, and the animals were studied with transthoracic echocardiography. All echocardiographic parameters were recorded before creation of bilateral arterio-venous fistulas (week 0) and repeated serially by the same veterinary physician at 3rd week, 6th week and at 12th week thereafter. Bilateral shunt occlusion was confirmed at one dog. Therefore, the data obtained from this animal were excluded from the final analysis. In the other 11 dogs, both AV fistulas functioned well till the end of the study, and this was also confirmed by autopsies as well.

Compared to the measurements obtained before the operation (week 0), the data obtained at the end of the experimental period showed significantly increased left ventricular volume measured by 2D-echo (from 25.1 cm³ to 43.8 cm³ p<0.0001 in diastole and from 8.6 cm³ to 16.8 cm³ p<0.001 in systole), and left ventricular diameter measured by M-mode echocardiography (from 26.2 mm to 32.6 mm p<0.0001 in diastole and from 17.1 mm to 20.6 mm p<0.001 in systole). The size of the left atrium has also increased in transversal (from 29.2 mm to 33.6 mm p<0.01) but not in longitudinal diameter. In spite of a significant cardiac chamber dilatation over the 12 week period, left ventricular systolic functional variables (fractional shortening, FS % and ejection fraction, EF %), and also the left ventricular systolic and diastolic free wall thickness have remained unchanged.

Over the twelve-week period, we have observed cardiac chamber dilatation, which developed gradually and progressively. Although the low-volume fistulas did not cause clinically manifested heart failure in our experiment, our serial studies allowed us to make observations in the early phase of the cardiac dilatation process. In our findings, it may particularly be important, that the left atrial dilatation occurred without development of mitral regurgitation and/or detectable left ventricular dysfunction.

We have successfully demonstrated that chronic volume overload induced by bilateral femoral AV fistulas resulted in progressive cardiac dilatation over a 12-week period in dogs. Although clinical heart failure and LV dysfunction did not develop, this model may be suitable for future morphological and biochemical research. Using serial echocardiographic studies, the structural and functional changes in the heart could be monitored easily and without pain

or discomfort to the animals, and therefore, it should be the method of choice to characterize the clinical stages of heart failure.

Two-dimensional echocardiographic measurements of the left atrium in dogs with cardiac disease

Echocardiography is an essential diagnostic tool for the assessment of cardiac function, anatomy and pathology. In the past two decades, echocardiographic examination protocols were focused on the determination of the parameters and systolic function of the left ventricle to conclude the severity of cardiac abnormalities by its evaluation. In the past few years, scientists have started to recognize the importance of the assessment of the left atrial size and function to determine the stage and prognosis of cardiac diseases.

Several studies have been made to demonstrate the prognostic importance of the left atrial size in canine cardiac patients. In the history of echocardiography, numerous techniques have been worked out for the assessment of the left atrium, but these methods proved to be laborious, time-consuming and not always easy to perform. By examining a study group of healthy dogs in our previous study, we have established a new technique to measure the left atrial size, just above the mitral annulus (La_{ama}), which can be found and determined easily by two-dimensional echocardiography. A very strong relationship was found between La_{r-l} (right-left diameter, measured at the widest point of the left atrium) and La_{ama} . La_{ama} could be substituted for La_{r-l} in cases, where determination of La_{r-l} is difficult. La_{r-l} can be calculated from La_{ama} according to the equation of $La_{r-l} / La_{ama} = 0,0004 * \text{Body Weight} + 1,0833$. Therefore, La_{r-l} is larger than La_{ama} by approx. 8%. The aim of our present study was to verify the validity of this measurement technique in dogs with left atrial enlargement. According to our assumptions, in the case of atrial enlargement the La_{r-l} would increase in a faster manner than La_{ama} . This hypothesis could question the relevance of the La_{r-l} / La_{ama} proportion in dogs with cardiac disease.

During the research, altogether 31 dogs suffering from cardiopathy associated with left atrial enlargement were examined. The dogs represented 17 different breeds and included mixed-breed dogs as well. By echocardiography 26 dogs were diagnosed with mitral endocardiosis (ME), while the remaining 5 dogs suffered from dilated cardiomyopathy (DCM). The standard

echocardiographic views were taken up from the right parasternal view. The criterion of including dogs in the experiment was that during the 2DE measurement the La/Ao ratio had to reach or exceed 1.7.

Based on the results of our examinations, we can conclude (similarly to the results of healthy dogs) that La_{r-l} / La_{ama} proportion is independent of body weight ($R^2=0,0006$) and of age ($R^2=0,0012$) of the individuals. We found a significant linear relationship between La_{ama} and La/Ao (the proportion that expresses the severity of atrial enlargement): $La_{ama} = 1,2238 La/Ao + 1,1608$ ($R^2=0,021$; $p<0,01$). There was also a positive linear relationship between La_{r-l} and La/Ao: $La_{r-l} = 1,6876 La/Ao + 1,2648$ ($R^2=0,27$; $p<0,005$). In dogs with cardiac disease, the La_{r-l} / La_{ama} proportion shows no significant relation to La/Ao index ($R^2=0,028$). Thus, La_{r-l} / La_{ama} is independent of the severity of atrial enlargement. In the present study, we have concluded that the equation can not be applied in canine cardiac patients in its original form, as worked out in our laboratory for healthy dogs. However, based on the strong relationship stated in the equation between La_{ama} and La_{r-l} , La_{ama} can still be substituted for La_{r-l} in the assessment of the left atrial size in dogs with cardiac abnormalities with the following modified formula: $La_{r-l} / La_{ama} = 1,31159$ (95% interval of confidence). Therefore, La_{r-l} is larger than La_{ama} by approx. 31%.

Echocardiographic and electrocardiographic examination of clinically healthy, conscious ferrets

With the increasing number of ferrets kept as pet animals, the demand for the accurate echocardiographic determination of different cardiac abnormalities arises more and more often. Our objective was to assess the feasibility of electrocardiography (ECG) and echocardiography performed on conscious ferrets and to establish reference values for this species under these conditions. Namely all ECG and echocardiographic results reported in the literature so far have been obtained in anaesthetized ferrets.

The ferrets included in the study were selected from healthy animals presented to our clinic for routine vaccination, microchip implantation or with minor non-cardiac related problems. Follow up exams were performed 3 years after completing the original studies and included searching the university database, telephone interviewing the owners and repeating the ECG

exams in those ferrets where an arrhythmia was detected formerly. Echocardiographic and ECG examinations were carried out in all animals without sedation.

End-systolic and end-diastolic left ventricular diameters, left ventricular and interventricular septal thicknesses were measured by M-mode echocardiography, while left atrial, aortic, and pulmonary trunk diameters were determined by two-dimensional echocardiography. In some animals the maximum velocities of blood flow in the aorta and the pulmonary trunk were also measured by spectral Doppler. ECG exams were performed by using limb leads both in right lateral recumbent and in the so called "hanging" position. During the ECG examinations, the occurrences, directions, durations and amplitudes of the P, QRS and T waves and duration of the PR and QT-intervals were described for all six leads.

There were originally 53 ferrets examined, however in four animals cardiac diseases (mitral valve disease in three, dilated cardiomyopathy in one animal), were diagnosed during the original or during the follow up exams and were excluded. In one ferret supraventricular extrasystoles were detected during the initial ECG-exam and the animal was lost to follow up. Despite the fact that this ferret was free of clinical signs and no morphological changes were seen during echocardiography, eventually decision was made to exclude the data of this animal, too. The remaining 48 ferrets formed the final study population. There were 29 females (19 intact and 10 neutered) and 19 males (11 intact and 8 castrated). Their age ranged between 10 months and 7 years (median: 1,5 yrs). They weighed between 0,6-2,3 kg. (mean: $1,1 \pm 0,4$ kg). There were no difference in the mean ages of the two sexes, however males were significantly ($p < 0,001$) heavier than females, $1,47 \pm 0,36$ kg and $0,79 \pm 0,14$ kg, respectively.

Generally the ferrets tolerated well the echocardiographic exam, thus echocardiography was possible to be performed in 46 of the 48 ferrets (96%). All of the measured M-mode and 2DE parameters (except the FS value) were significantly different between males and females ($p < 0,02$). The ECG-exam could be successfully performed in 43 of the 48 ferrets (90%). Their heart rate varied between 210-405 bpm, females had significantly higher heart rate than males (300 ± 58 bpm vs. 260 ± 34 bpm, $p < 0,01$). Most of the animals showed sinus rhythm during the exam, sinus arrhythmia was detected in only about 10 % of the ferrets.

Ferrets kept as pets and accustomed to the human hand can be restrained easily and examined without sedation or anaesthesia. The findings of this study indicate that both echocardiography and ECG can be performed in conscious ferrets. We have demonstrated that both echocardiography and ECG are useful methods for diagnosing cardiac changes

even in conscious ferrets, and the results obtained can be used as reference values in the future.

New scientific results

1. We have successfully demonstrated, that the volume overload induced by bilateral femoral AV fistulas resulted in chronic (but progressive) cardiac dilatation in dogs.
2. We have described first time in the literature, the long-term - over 3 months - echocardiographic follow-up of consequences of induced chronic volume overload in dogs. During our research, we provided new data from the changes of cardiac parameters over the time.
3. In our study on dogs with atrial enlargement, a significant positive, linear correlation has been demonstrated between the left atrial right-to-left diameter (La_{r-l}) and the La/Ao ratio determined in end-systole and indicating the severity of atrial enlargement, the diameter of the left atrium just above the mitral annulus (La_{ama}) also shows a significant positive, linear correlation with the La/Ao . We have also established that the La_{r-l} diameter depends on the La/Ao ratio more than the La_{ama} diameter. Thus, La_{r-l} (the internal diameter measured at the midline of the atrium) is a more sensitive indicator of changes in atrial dimensions. The correlations can be described by the following linear equations:

$$La_{r-l} = 1.6876 La/Ao + 1.2648; (R^2=0.27; p<0.005)$$

$$La_{ama} = 1.2238 La/Ao + 1.1608; (R^2=0.21; p<0.01)$$

4. By examining the ratio of the two diameters in dogs with cardiac disease, we found that, despite the slightly differing sensitivity, the La_{r-l}/La_{ama} ratio did not significantly depend on the La/Ao ratio ($R^2=0.028$), i.e. the La_{r-l}/La_{ama} ratio was constant, irrespective of the severity of cardiac disease and the extent of left atrial enlargement. In this way we can state that the diameter of the left atrium measured just above the mitral annulus (La_{ama}) can be used in dogs with cardiac disease as well. The ratio of atrial diameters can be described by the following equation:

$$La_{r-l}/La_{ama} = 1.31159 \text{ (in a confidence interval of 95\%)}$$

5. We have established, that in dogs suffering from cardiac disease with left atrial enlargement the La_{r-l}/La_{ama} ratio does not significantly depend on the dog's body weight

($R^2=0,0006$), and that the La_{r-l}/La_{ama} ratio is independent of the cardiopathic dog's age as well ($R^2=0.0012$)

6. We have determined - first time in the literature - the echocardiographic parameters of conscious, healthy ferrets, and we have also presented normal reference values which can be of international interest.
7. We have determined - first time in the literature - the ECG parameters of conscious, healthy ferrets, and we have also presented normal reference values which can be of international interest.
8. We have developed a new, till now not described method for restraining ferrets for ECG examination by holding the skin of the neck and hanging in the air vertically. In this way, the ferret remains completely still. This restraining makes the ECG examination quite comfortable and does not influence the ECG parameters in comparison with the traditional recumbency method.

Publications related to the dissertation

Dudás Györki Z, Kollár A, Manczur F, Kékesi V, Vörös K (2007): Echocardiographic characterisation of cardiac dilatation induced by volume overload in a canine experimental model. Acta Vet. Hung., **55**, 41-50.

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Dudás Györki Z, Szabó Z, Manczur F, Vörös K: Echocardiographic and electrocardiographic examination of clinically healthy, conscious ferrets. Under consideration for publication: J. Small Anim. Pract. 2010. május.