The diagnostic significance of plasma N-terminal pro-B type natriuretic peptide concentration in dogs and cats with cardiac diseases

Summary of Doctoral Thesis

Yoshinori Tominaga

(Supervised by Prof. Naoyuki Takemura)

Graduate School of Veterinary Medicine and Life Science
Nippon Veterinary and Life Science University

Cardiac diseases in dogs and cats are one of the most common disorder in clinical settings. Mitral valve insufficiency (MVI) in dogs and hypertrophic cardiomyopathy (HCM) in cats are the most common. These diseases can lead to congestive heart failure (CHF) with poor prognosis.

History-taking, physical examination, electrocardiogram, thoracic radiography and echocardiography are usually performed as diagnostic examinations for dogs and cats with cardiac diseases. N-terminal pro B type natriuretic peptide (NT-proBNP) used as cardiac biomarker in human medicine is also available in dogs and cats, and contradicting results for its diagnostic significance have been reported in these species to date. One cause of such controversy might result from the unknown factors affecting plasma NT-proBNP concentration in dogs and cats. Therefore, the purposes of the present study were to investigate various factors affecting plasma NT-proBNP concentration, and to establish the diagnostic significance of plasma NT-proBNP concentration for evaluating MVI in dogs and HCM in cats.

1. Intra- and inter-assay variations in canine and feline plasma NT-proBNP concentration (Chapter 2)

Intra- and inter-assay variations are significant to determine whether the variation of plasma NT-proBNP concentration resulted from hemodynamics or measurement procedure when there were variations in plasma NT-proBNP concentration in same case. In addition, necessity to add aprotinin to the plasma were also determined.

The plasma obtained from 5 dogs and 5 cats were used. In the evaluation of intra-assay variation, the plasma added to ethylenediamine-tetraacetic acid (EDTA) was divided into 10 tubes, and the plasma NT-proBNP concentrations were simultaneously measured. In the

evaluation of inter-assay variation, plasma NT-proBNP concentrations were measured 10 times at interval over 1 day. Mean, standard deviation (SD) and coefficient of variance (CV) were calculated. Then, the plasma NT-proBNP concentration was measured using the plasma added to EDTA and aprotinin, and the concentrations were compared with the concentrations measured using the plasma added EDTA.

The medians of CV indicating intra- and inter-assay variations in plasma NT-proBNP concentrations were 11.4 and 19.9% in dogs, and 10.6 and 16.9% in cats. These variations were larger in those in humans, however comparable to those from dogs and cats by another reports. Inter- and intra- assay variations were similar between sample added to EDTA and sample added to EDTA and aprotinin. There was the tendency that plasma NT-proBNP concentration was less variable in the sample added to EDTA.

Based on these results, it was decided that the canine and feline plasma added to EDTA were used in further research in the present study. Variation of about 20% in plasma NT-proBNP concentration due to measurement procedure was confirmed in this chapter.

2. Daily and weekly variations of, and effects of dietary intake and walking on plasma NT-proBNP concentration in clinically healthy dogs and cats (Chapter 3)

Existence and absence of daily and weekly variations in plasma NT-proBNP concentration were determined using clinically healthy dogs (n=7) and cats (n=5), and effects of dietary intake and 15 minutes walking were observed only in clinically healthy dogs (n=7).

The plasma were obtained every 3 hours, and significance of daily variation was determined by plasma NT-proBNP concentration at each time.

The degree of daily variation was determined by CV. The plasma were obtained every week, and the presence and the degree of weekly variation were analyzed. In the evaluations of effects of diet intake or walking, the plasma was obtained before diet intake or walking, and 5, 15, 30, 60, 90 120 and 180 minutes after diet intake or walking. The dogs were made to walk for 15 minutes at the speed similar to human walking.

Although there were insignificant daily variations in both species, daily or weekly variation of about 20% in dogs and 35% in cats were confirmed. In addition, dietary intake and walking did not affect plasma NT-proBNP concentration.

Based on these results, it was concluded that the time for sampling and dietary intake and walking were not required to consider for the measurement of canine and feline plasma NT-proBNP concentrations. However, it was advised that the intra-individual variation of 20-35% should be considered when plasma NT-proBNP concentration was interpreted in clinical setting.

3. Effect of glomerular filtration rate on plasma NT-proBNP concentration in dogs and cats (Chapter 4)

Because circulating NT-proBNP is excreted only from the kidney, plasma NT-proBNP concentration may be affect by glomerular filtration rate (GFR). However, association of the concentration and GFR were not investigated in dogs and cats to date. Thus, the effect of GFR on plasma NT-proBNP concentration was investigated using 73 dogs and 34 cats with various GFR and without cardiac disease, which were presented to the cardiology service in the Animal Medical Center, Nippon Veterinary and Animal Science University.

As the results, plasma NT-proBNP concentration significantly and inversely correlated with GFR in dogs but not in cats. Plasma NT-proBNP concentration significantly increased in cats with moderator to severely reduced GFR. In some animal, plasma NT-proBNP concentration exceeded cutoff value for detection of animals with possible cardiac disease.

These results indicated that GFR should be considered when plasma NT-proBNP concentration was used as cardiac biomarker. However, it was impractical that measurement of GFR in all clinical cases, and thus, plasma NT-proBNP concentration should be interpreted with simultaneous plasma creatinine concentration

4. The diagnostic significance of plasma NT-proBNP concentration in dogs with MVI (Chapter 5)

In this chapter, the diagnostic significance of plasma NT-proBNP concentration in dogs with MVI, dogs with MVI and tricuspid valve insufficiency (TVI), and dogs with MVI, TVI and pulmonary hypertension PH) secondary to MVI were investigated. In this study, 270 dogs presented to the cardiology service in Animal Medical Center, Nippon Veterinary and Animal Science University were used.

In dogs with MVI, plasma NT-proBNP concentration increased in association with cardiac enlargement due to MVI. However, plasma NT-proBNP concentration in dogs without cardiac enlargement, indicating the concentration was less significance as screening test in such dogs. Since plasma NT-proBNP concentration elevated in association with increases in volume overload of the left atrium and ventricle, the concentration might be useful for continuous monitoring for left-heart volume overload. In addition, plasma NT-proBNP concentration was significantly higher in dogs with MVI, TVI and secondary PH than that in

dogs with MVI alone. In dogs classified as International Small Animal Cardiac Health Council stage IIIa, plasma NT-proBNP concentration was found to be sensitive and less specific to detect complication of TVI and PH secondary to MVI. Echocardiography would be essential to confirm the existence of TVI and PH.

5. The diagnostic significance of plasma NT-proBNP concentration in cats with HCM (Chapter 6)

In this chapter, the diagnostic significance of plasma NT-proBNP concentration, and the association with the concentration and several echocardiographic variables were investigated using 95 cats presented to the cardiology service in the Animal Medical Center, Nippon Veterinary and Life Science University. Result in this chapter indicated that plasma NT-proBNP concentration increased in association with existence of CHF, left ventricular hypertrophy and left atrial dilation. It was also confirmed that plasma NT-proBNP concentration could detect even cats with asymptomatic HCM with reliable sensitivity (83.9%) and specificity (93.9%). It was noteworthy that cats with asymptomatic HCM could be detected using plasma NT-proBNP concentration, because such cats could not be detected by using clinical examination other than echocardiography. Moreover, plasma NT-proBNP concentration might be valuable to follow the degree of ventricular hypertrophy and atrial distention in same cat.

In conclusion, it was considered that the diagnostic value of plasma NT-proBNP concentration was more significant in cat with HCM than in dogs with MVI. Plasma NT-proBNP concentration failed to detect dogs with mild MVI without cardiac enlargement and dogs with complication of TVI and PH. In contrast, clinical value of plasma NT-proBNP

concentration was more significant in cats with HCM. Especially, it would be most important finding in the present study that plasma NT-proBNP concentration could detect cats having asymptomatic HCM with acceptable sensitivity and specificity. Cats with HCM suddenly developed CHF and/or arterial thromboembolism, and HCM was found to be inheritance disease in some feline breeds. Including plasma NT-proBNP concentration in feline screening health examination might be helpful in early detection and therapeutic intervention for HCM.