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Investigation into the use of plasma NT-proBNP concentration to screen for feline hypertrophic cardiomyopathy

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Abstract *Objective:* To evaluate the utility of feline NT-proBNP plasma concentration [NT-proBNP] as a screening tool for cats with subclinical hypertrophic cardiomyopathy (HCM).
Animals, materials and methods: Forty adult Maine Coon or Maine Coon crossbred cats from the feline HCM research colony at the University of California, Davis were studied. All cats had previously been genotyped as heterozygous or negative for the A31P myosin binding protein C (MYBPC) mutation. Echocardiograms were performed to assess the severity of HCM in each cat. Blood samples were collected for evaluation of [NT-proBNP].
Results: In these cats with severe HCM, [NT-proBNP] was significantly elevated ($P < 0.0001$) when compared to all other groups of cats and an [NT-proBNP] > 44 pmol/L accurately predicted the presence of severe HCM. However, [NT-proBNP] was not increased in cats with moderate or equivocal HCM when compared to normal cats. Cats heterozygous for the MYBPC mutation had a significantly elevated [NT-proBNP] when compared to cats without the A31P mutation ($P = 0.028$).
Conclusions: Measurement of [NT-proBNP] has a high sensitivity and specificity as a means of detecting severe HCM in cats, but it is not sensitive for the identification of moderate HCM as judged by the evaluation of Maine Coon and Maine Coon cross cats in our colony. Consequently, we conclude that this test cannot be used to screen cats for the presence of mild to moderate HCM.

Introduction

Feline hypertrophic cardiomyopathy (HCM) is a common, primary myocardial disease characterized

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by thickening of the left ventricular myocardium. It is either idiopathic or due to mutations in cardiac myosin binding protein C in Maine Coon and Ragdoll cats.[1,2] HCM ranges in severity from mild to severe. Cats with mild to moderate disease generally show no clinical signs (i.e., they are subclinical) while those with severe disease range from having no clinical signs to experiencing congestive heart failure, aortic thromboembolism, and sudden death.

The diagnosis of feline HCM is made using echocardiography, although it is a diagnosis of exclusion. An unequivocal diagnosis of HCM can be made when the entire LV wall or some region is 6 mm or more thick in the absence of hyperthyroidism, systemic hypertension and severe dehydration.[3] The thickening is almost always accompanied by moderate to severe papillary muscle enlargement in cats. Commonly there is end-systolic cavity obliteration. Systolic anterior motion of the mitral valve may or may not be present. The left atrium may or may not be enlarged. Other echocardiographic techniques, including assessment of transmitral flow via pulsed wave Doppler and Doppler tissue imaging, may be useful for identifying the diastolic dysfunction often present with severe HCM.[4]

Because feline HCM is common in certain breeds of cats, screening for this disease is a frequent request of breeders who want to attempt to reduce the incidence of HCM in their line(s). Screening for HCM is fraught with difficulties. The sensitivity and specificity of auscultation in detecting cardiac disease in cats is compromised by the absence of auscultatory abnormalities in many cats with HCM, especially those with mild to moderate disease, and the occasional presence of a physiologic murmur, most commonly due to dynamic right ventricular outflow tract obstruction, in cats.[5,6] The sensitivity of thoracic radiography for diagnosing even severe HCM in cats is limited due to the concentric nature of the left ventricular hypertrophy coupled with the more cranial location of the left atrium in cats when compared to dogs.[3] In addition, the specificity of thoracic radiography for HCM is very poor. As such, screening for HCM has historically required an echocardiographic examination by an experienced individual, which is often an expensive and time consuming process.

Consequently, there is an obvious desire for a simpler, more readily available, and less expensive tool to screen cats for HCM. Serum or plasma biomarkers are widely utilized in human medicine to assess cardiac disease. Recently, a plasma assay for the feline N-terminal of the prohormone of brain natriuretic peptide (NT-proBNP) has become available. This has sparked profound interest in exploring the usefulness of this biomarker in feline cardiac disease. BNP is a peptide that is synthesized in the cardiac atria and ventricles. The putative reason for increased expression of BNP is myocardial stretch. BNP is initially expressed as a prohormone (proBNP).[7] ProBNP is cleaved and released from myocytes as active BNP and the inactive N-terminal or NT-proBNP. NT-proBNP is less labile with a longer plasma half life compared to active BNP. Although NT-proBNP is not the active polypeptide product, its plasma concentration reflects the plasma concentration of active BNP ([BNP]).[8,9] Therefore, it has been utilized as a more stable marker of BNP activity.

In humans with HCM, an elevated plasma NT-proBNP concentration ([NT-proBNP]) has been associated with various features of the disease.[10,11] Specifically, a positive correlation has been found between [NT-proBNP] and several variables including NYHA class of heart failure, left atrial size, severity of diastolic dysfunction, left ventricular outflow tract gradient and severity of left ventricular hypertrophy.[12–14] Examination of the role of cardiac biomarkers in feline cardiac disease as predictors of disease severity has been limited. The roles of N-terminal and C-terminal atrial natriuretic peptide (ANP), NT-proBNP, cardiac troponin I, and plasma endothelin reactivity have been explored in various feline cardiac diseases, including HCM.[15–20] Cats with subclinical HCM were included in some of these studies, however subject numbers and the description regarding severity of HCM have been limited.

The present study was designed to examine plasma NT-proBNP concentration in cats with moderate to severe HCM in a colony of cats with HCM where the disease has been carefully characterized over years in each cat. The specific aim of the study was to determine the feasibility of using plasma NT-proBNP concentration to identify cats with moderate or severe disease.

Animals, materials and methods

Animals

The study included adult Maine Coon and Main Coon crossbred cats from the feline HCM research colony at the University of California, Davis. Animals were cared for according to the guidelines in the NIH Guide for the Care and Use of Laboratory Animals. All cats had previously been genotyped as heterozygous or negative for the A31P myosin binding