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Biologic variability of N-terminal pro-brain natriuretic peptide in healthy dogs and dogs with myxomatous mitral valve disease

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Abstract *Introduction:* To determine the biologic variability of N-terminal pro-brain natriuretic peptide (NTproBNP) in healthy dogs and dogs with various stages of myxomatous mitral valve disease (MMVD).
Animals: Thirty-eight privately owned dogs: 28 with MMVD and 10 healthy controls.
Materials and methods: Prospective clinical study with comprehensive evaluation used to group dogs as healthy or into three stages of MMVD based on current guidelines. NTproBNP was measured hourly, daily, and weekly. For each group, analytical (CV_A), within-subject (CV_I), and between-subject (CV_G) coefficients of variability were calculated in addition to percent critical change value (CCV) and index of individuality (IoI).
Results: For healthy dogs, calculated NTproBNP values were: $CV_A = 4.2\%$; $CV_I = 25.2\%$; $CV_G = 49.3\%$; IoI = 0.52, and CCV = 70.8%. For dogs with MMVD, calculated NTproBNP values were: $CV_A = 6.2\%$; $CV_I = 20.0\%$; $CV_G = 61.3\%$; IoI = 0.34, and CCV = 58.2%.

The study was performed at the Veterinary Medical Teaching Hospital, Texas A&M University, College Station, TX.
The data from this study were presented in oral abstract form at the 2014 ACVIM Forum in Nashville, TN.

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Conclusions: Biologic variability affects NTproBNP concentrations in healthy dogs and dogs with MMVD. Monitoring serial individual changes in NTproBNP may be clinically relevant in addition to using population-based reference ranges to determine changes in disease status.

Abbreviations

ACVIM	American College of Veterinary Internal Medicine
Ao	aorta
BV	biologic variability
CCV	critical change value for percent difference in biomarker value
CV	coefficient of variation
CV_A	analytical coefficient of variation
CV_G	between-subject coefficient of variation
CV_I	within-subject coefficient of variation
IoI	index of individuality
LA	left atrium
LVID	left ventricular internal dimension
MMVD	myxomatous mitral valve disease
NTproBNP	N-terminal pro-brain natriuretic peptide
VHS	vertebral heart size

Introduction

Biologic variability (BV) is defined as the change in analyte concentration that occurs independently of the disease status of the patient [1]. Specifically, this refers to changes in analyte concentration when multiple samples are obtained from either a healthy subject or from a patient with stable disease [1,2]. Treatment recommendations and prognosis frequently depend on disease status, therefore establishing the BV is necessary for understanding the clinical importance of changes in the longitudinal measurement of analytes.

Myxomatous mitral valve disease (MMVD) is the most common cardiac disease in dogs and is extensively studied in veterinary medicine [3—5]. Studies in dogs with MMVD have investigated the clinical utility of the circulating cardiac biomarker N-terminal pro-brain natriuretic peptide (NTproBNP) [6—9]. Elevated NTproBNP concentrations have been associated with an increased hazard of congestive heart failure and mortality in dogs with MMVD, highlighting its potential value in longitudinal evaluation of this disease [6,8,10].

In humans, NTproBNP has been studied in acquired cardiac disease [11—14], and BV is acknowledged as an important component of interpreting longitudinal changes when assessing disease [15—17]. Knowledge of NTproBNP BV has proven useful in the accurate interpretation of changes in both healthy humans and those with cardiac disease. Evaluation of the BV of NTproBNP in dogs is limited [18,19].

The objectives of this study were to measure NTproBNP in healthy dogs and dogs with MMVD classified into American College of Veterinary Internal Medicine (ACVIM) stages B1, B2, or C-stable in order to estimate BV and calculate the Index of Individuality (IoI) of this analyte to determine if population-based reference ranges are appropriate. A secondary objective was to calculate the critical change value (CCV) for percent difference in NTproBNP concentration needed in order to suggest a change in disease in each group of dogs.

Materials and methods

Animals

Healthy dogs were prospectively recruited from staff and students, and dogs with MMVD were prospectively recruited from the clinical caseload of the Texas A&M University Veterinary Medical Teaching Hospital from August 2012 to August 2013. The study protocol was approved by the University Institutional Animal Use and Care Committee, and informed consent was obtained from all owners. Inclusion criteria included dogs aged >1 year, weighing between 5.0 and 15.0 kg, without any evidence of clinically important systemic disease. All dogs underwent diagnostic testing immediately prior to entry into the study. Diagnostic tests included physical examination, cardiac auscultation, echocardiography, electrocardiography, indirect blood pressure measurement, serum biochemical analysis, and MMVD dogs additionally had thoracic radiography

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