Journal of Veterinary Cardiology (2012) ■, ■–■

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Journal of Veterinary Cardiology
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Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: The PREDICT cohort study

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Received 31 October 2011; received in revised form 18 January 2012; accepted 19 January 2012

KEYWORDS
Natriuretic peptide;
Mitral regurgitation;
BNP

Abstract *Objective:* To identify risk factors for first-onset congestive heart failure (CHF) in dogs with degenerative mitral valve disease (DMVD).
Animals: Eighty-two dogs with and without CHF secondary to DMVD were retrospectively assigned to a derivation cohort. Sixty-five dogs with asymptomatic DMVD were recruited into a prospective validation cohort.

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1760-2734/$ - see front matter
doi:10.1016/j.jvc.2012.01.008

Please cite this article in press as: Reynolds CA, et al., Prediction of first onset of congestive heart failure in dogs with degenerative mitral valve disease: The PREDICT cohort study, Journal of Veterinary Cardiology (2012), doi:10.1016/j.jvc.2012.01.008

Methods: Variables associated with risk of CHF in dogs were identified in a derivation cohort and used to construct a predictive model, which was then prospectively tested through longitudinal examination of a validation cohort.
Results: Logistic regression analysis of the derivation cohort yielded a predictive model that included the left atrial to aortic root dimension ratio (LA:Ao) and plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP). When this model was prospectively applied to the validation cohort, it correctly predicted first-onset of CHF in 72.5% of cases. Analysis of the validation cohort revealed that plasma NT-proBNP concentration and indexed left ventricular end-diastolic diameter (LVIDd:Ao) were independent risk factors for development of first-onset CHF in dogs with DMVD (NT-proBNP $\geq$1500 pmol/L, odds ratio (OR), 5.76, 95% confidence interval (CI), 1.37–24.28, $P = 0.017$; LVIDd:Ao $\geq$3, OR, 6.11, 95% CI, 1.09–34.05, $P = 0.039$).
Conclusions: Measures of left heart size and plasma NT-proBNP concentration independently estimate risk of first-onset of CHF in dogs with DMVD. These parameters can contribute to the management of dogs with DMVD.

Abbreviations

AUC	area under the curve
BNP	B-type natriuretic peptide
CHF	congestive heart failure
CI	confidence interval
DMVD	degenerative mitral valve disease
LA:Ao	left atrial to aortic root dimension ratio
LVIDd	left ventricular internal diameter at end-diastole
LVIDd:Ao	left ventricular internal diameter at end-diastole indexed to aortic root
LVIDs	left ventricular internal diameter at end-systole
LVIDs:Ao	left ventricular internal diameter at end-systole indexed to aortic root
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OR	odds ratio
ROC	receiver operating characteristic
TR	tricuspid regurgitation
VHS	vertebral heart size

Introduction

Degenerative mitral valve disease (DMVD) is the most common cardiac disease in the canine population and is present in more than one-third of dogs over ten years of age.[1] The course of DMVD is highly variable. From the time of initial identification of a characteristic murmur, some dogs rapidly progress to congestive heart failure (CHF) while others demonstrate a very slow progression and CHF is not experienced within the dog's lifetime.[2] In the asymptomatic dog, veterinarians traditionally have assessed disease progression and prognosis using patient parameters including heart rate, murmur grade, echocardiographic and radiographic heart size, and routine blood testing[2]; however, the basis underlying these assessments for risk stratification requires validation.

In humans with DMVD, both B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) predict future morbidity and mortality.[3,4] Increased cardiac stress is a major stimulus for myocardial production and release of these hormones.[5] Circulating BNP and NT-proBNP concentrations increase as severity of DMVD worsens,[6,7] and elevated blood BNP level is independently associated with risk of future CHF in human patients with asymptomatic DMVD.[8] It is well established that BNP and NT-proBNP are significantly elevated in dogs with DMVD.[9–13] Concentration of BNP[14] and radiographic heart size[15,16] increase as DMVD progresses, and both heart size and NT-proBNP[2,17–19] are associated with survival; however, the utility of these variables to predict first-onset of CHF has not been determined. Thus, we sought to evaluate whether measurement of selected clinical parameters including those obtained from echocardiography, radiography, physical examination, and NT-proBNP measurement in dogs with asymptomatic DMVD predict risk of CHF.

Animals, materials and methods

The study was designed as a derivation and validation cohort study to first identify clinical

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variables that predict first-onset of CHF in dogs with asymptomatic DMVD, followed by recruitment of a prospective cohort to validate the developed hypothesis.

Retrospective derivation study

Medical records between January 2006 and December 2007 from the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania were retrospectively searched. Inclusion criteria involved a new or historical diagnosis of DMVD, an echocardiographic exam, thoracic radiographs, and results of plasma NT-proBNP assay. Dogs were assigned to group 1 if diagnosed with CHF based on both clinical signs and radiographic evidence. Dogs were assigned to group 2 if diagnosed with asymptomatic DMVD. Baseline data recorded for each dog included the following variables: age, heart rate, Doppler echocardiographic velocity of tricuspid regurgitation (TR) (if present), radiographic vertebral heart size (VHS), 2D echocardiographic left atrial to aortic root diameter ratio (LA:Ao) and left ventricular dimension at end-diastole (LVIDd) and end-systole (LVIDs), and plasma NT-proBNP concentration.

Prospective validation study

Dogs with an echocardiographic diagnosis of DMVD were prospectively recruited from November 2006 to September 2010 from seven referral or teaching hospitals, including the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (Philadelphia, PA), the Cummings School of Veterinary Medicine at Tufts University (North Grafton, MA), Chesapeake Veterinary Cardiology Associates (Vienna, VA; Richmond, VA), MedVet Medical and Cancer Centers for Pets (Columbus, OH), Austin Heart Vet (Austin, TX), Veterinary Medical Teaching Hospital of the Texas A&M University (College Station, TX), and the Veterinary Medical Teaching Hospital of the University of Wisconsin (Madison, WI). At each site, either a board-certified cardiologist or a resident-in-training under direct supervision of board-certified cardiologist served as the patient's primary clinician. Cardiac status of all dogs recruited into the study was modified American College of Cardiology/American Heart Association stage B2 (heart disease with evidence of cardiac remodeling/enlargement).[20] We defined cardiac remodeling as an LA:Ao of $\geq$1.6 based upon 2D echocardiographic examination.[21] Dogs were excluded that had current or previous history of CHF, who received diuretics, or who had significant concurrent systemic disease. Each dog underwent physical examination, 2D and Doppler echocardiographic exam, thoracic radiographs, and plasma NT-proBNP assay. Data, including body weight, murmur grade, heart rate, VHS, LVIDd, LVIDs, LA:Ao, and TR velocity (if present) were recorded on a standardized data collection form. To assay for NT-proBNP concentration, 2–5 mL of blood were collected in EDTA tubes, centrifuged, and the resulting plasma separated within 20 min of collection. Plasma was stored at −20 °C until batch analysis of NT-proBNP[i], generally within 90 days after collection. Clinicians were blinded to the results of the NT-proBNP data at the time of the dog's examination and data collection. Following the baseline examination, dogs were re-examined at approximately 3–12 month intervals at the discretion of the primary clinician. During each re-examination, the aforementioned diagnostic tests were repeated. The study endpoint was defined as the onset of pulmonary edema based upon radiographic findings, and clinical signs of cough, respiratory distress, and/or increased respiratory rate or effort, which in the opinion of the primary clinician necessitated medical therapy (Fig. 1).

Statistical methods

Descriptive statistics were calculated. Normality was tested using the Kolmogorov–Smirnow test. Normally distributed continuous data were expressed as mean and standard deviation. Non-normal data were expressed as median value and interquartile range. Categorical data were expressed as frequencies. NT-proBNP results reported as >3000 pmol/L were coded as 3001 pmol/L. Left ventricular echocardiographic dimensions in end-diastole and end-systole were indexed to the aortic root diameter (LVIDd:Ao and LVIDs:Ao, respectively).

The study design utilized a retrospective derivation cohort to identify candidate variables and construct a predictive model of risk. Data from the derivation portion of the study were analyzed as follows: differences in variables between groups were analyzed by chi-square, Mann–Whitney, or unpaired *t*-tests. Logistic regression analyses were performed to evaluate factors associated with the presence of CHF. Univariate analysis was performed and factors with a Wald test *P*-value <0.20 were subsequently tested in the multivariable

[i] CardioPet NT-proBNP assay, IDEXX Laboratories, Westbrook, ME, USA.

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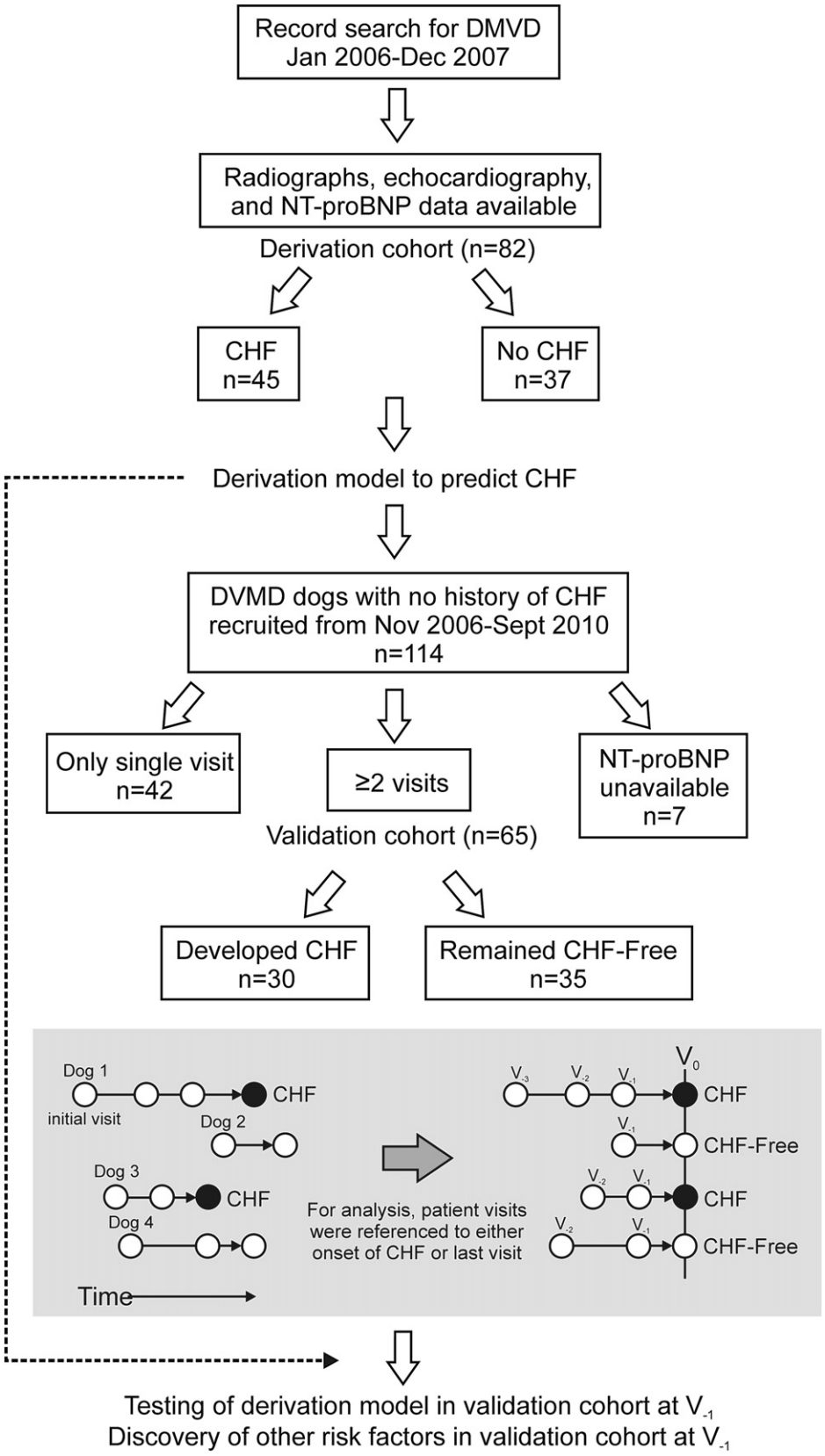

Figure 1 Flow diagram of the derivation and validation study investigating risk factors for first-onset of congestive heart failure in dogs with asymptomatic degenerative mitral valve disease. A schematic of how visits from individual dogs recruited into the study at different time points were referenced to a standard time point (V_0) for analysis is shown in the gray box. See text for more details. DMVD, degenerative mitral valve disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CHF, congestive heart failure.

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model. Variables were retained in a forward stepwise multivariate logistic regression model based on a Wald test *P*-value $\leq$0.05 or if found to be a confounder (changing model coefficients by >15%). Model fit was tested with Hosmer–Lemeshaw goodness of fit test. A receiver operating characteristic (ROC) curve was generated to evaluate the model for predicting whether an animal was in CHF. The ROC curve represents the relationship between the true positive rate (the probability of classifying a dog with CHF as having CHF [i.e., sensitivity]) and the false positive rate (the probability of classifying a dog without CHF as having CHF [i.e., 1-specificity]) for each possible cutoff value. The area under the curve (AUC) for the ROC curve is a global summary statistic of the predictive value across all possible cut points. This allows arbitrary classification of a test as highly accurate ($0.9 < AUC < 1$) or moderately accurate ($0.7 < AUC \leq 0.9$). Overall accuracy of prediction (i.e., ability to correctly predict presence or absence of CHF at or prior to the next visit) was calculated as the percentage of cases correctly predicted.

The validity of the derivation model was then prospectively tested in a cohort of dogs recruited into a longitudinal multicenter study. To assess performance of the retrospective model with respect to predicting CHF, an ROC curve was constructed and the corresponding AUC calculated. The sensitivity and specificity of various cutoff points were examined. The relative risk of CHF in patients above and below the cutoff points was determined. Logistic regression analyses were performed to evaluate factors associated with the presence of CHF. Variables collected at the time of onset of CHF or at the end of the study were designed as V_0 and each visit prior to this point was labeled with subsequent numbers (i.e., V_{-1}, V_{-2}, V_{-3}, etc), with V_{-1} being the visit immediately preceding onset of CHF or the end of the study, V_{-2} being the second to last visit immediately preceding V_0, etc. Univariate analysis was performed and factors with a Wald test *P*-value <0.20 were tested in a backwards stepwise multivariate logistic regression model. Factors were retained in the model based on a Wald test *P*-value $\leq$0.05 or if found to be a confounder (changing model coefficients by >15%). Two multivariate models were developed; one including echocardiographic variables and one without. For all analyses, $P < 0.05$ was considered significant. Commercial computer software[j,k,l] was used for statistical analysis.

[j] Systat 13, Systat software, Chicago, IL, USA.
[k] Prism 4.0, GraphPad Software, La Jolla, CA, USA.
[l] MedCalc 11.6.6.0, MedCalc Software, Mariakerke, Belgium.

Results

Retrospective study

Eighty-two dogs were retrospectively identified as meeting the entry criteria. These included 45 dogs (55%) in the CHF group 1 and 37 dogs (45%) in the non-CHF group 2 (Table 1). Results of univariate analysis are listed in Table 2. Variables that were significantly associated with presence of CHF from multivariate analysis included LA:Ao and NT-proBNP. Controlling for LA:Ao, a 500 pmol/L increase in BNP increased the OR for CHF by 2.5 (95% CI 1.2–5.0; $P = 0.013$). Controlling for NT-proBNP, a 0.5 increase in LA:Ao increased the OR for CHF by 10.6 (95% CI 2.0–56.7; $P = 0.006$). The model fit was deemed as good, with a goodness of fit *P*-value of 0.80. Analysis of the ROC curve indicated that the combination of LA:Ao and NT-proBNP was highly accurate in differentiating dogs with CHF from those without CHF with an AUC of 0.98. The regression equation that best described the probability of CHF was as follows:

$$\text{Probability of CHF} = 1/(1+\exp(-(-11.3 + (4.2*\text{LA:Ao}) + (0.0018*\text{NT-proBNP}))))$$

Prospective study

One-hundred and fourteen dogs were recruited. Forty-two dogs were excluded from further analysis having been examined at only a single time point, while 7 dogs were excluded due to unavailability of NT-proBNP results arising from an insufficient blood sample or technical reasons. The remaining 65 dogs (University of Pennsylvania, 15; MedVet, Medical and Cancer Centers for Pets, 11; Texas A&M University, 11; University of Wisconsin, 10; Chesapeake Veterinary Cardiology Associates, 9; Austin Heart Vet, 7; Tufts University, 2) qualified for analysis. Dogs were examined at baseline (initial visit) and then one or more times during the study, which ended on Dec 31, 2010. At V_{-1}, the median age was 10 yrs (9–11.5 yrs) and there were 38 females and 27 males. Median body weight was 8.5 kg (5.3–11.2 kg). The most common breeds were Cavalier King Charles Spaniel ($n = 16$), Chihuahua ($n = 8$), Shih Tzu ($n = 4$), miniature Schnauzer ($n = 3$), Springer Spaniel ($n = 3$), Cocker Spaniel ($n = 3$), and Australian shepherd ($n = 3$). Fourteen additional dogs were of mixed breeding.

Dogs were longitudinally examined until they developed CHF or completed the study. The

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Table 1 Descriptive statistics for radiographic, echocardiographic, and NT-proBNP variables in the derivation cohort. Group 1 is dogs with degenerative mitral valve disease with congestive heart failure. Group 2 is dogs with degenerative mitral valve disease without congestive heart failure. Values in brackets indicate number of observations in parameters with incomplete data.

	Group 1	Group 2	*P*-value
N	45	37	
Age (yrs) Median (IQR)	11 (10—12)	10 (8—12)	0.17
Gender	24 males (51%) 21 females (49%)	22 males (54%) 15 females (46%)	0.58
Breed	5 CKCS 5 Shih Tzu 4 Maltese 23 other purebred 5 mixed breed	5 CKCS 3 Beagle 18 other purebred 11 mixed breed	
Body weight (kg) Median (IQR)	8.5 (5.4—14)	10.9 (7.0—15.9)	0.27
Heart rate (bpm) Median (IQR)	145 (140—160) [22]	120 (100—135) [23]	<0.0001
VHS Mean (SD)	12.4 (1.0)	10.7 (1.0)	<0.0001
LVIDd:Ao Median (IQR)	2.80 (2.48—3.21) [27]	2.00 (1.78—2.27) [30]	<0.0001
LVIDs:Ao Median (IQR)	1.40 (1.21—1.73) [27]	1.16 (1.0—1.41) [30]	0.042
LA:Ao Median (IQR)	2.30 (2.00—2.70)	1.40 (1.20—1.68)	<0.0001
TR velocity (m/s) Mean (SD)	3.49 (0.62) [26]	2.89 (0.86) [27]	0.0054
NT-proBNP (pmol/L) Median (IQR)	2510 (1682—3001)	573 (284—963)	<0.0001

median number of visits for each dog was 3 (range 2—9 visits). The median follow-up time beyond the initial visit was 335 days (165—546 days). To account for the fact that dogs were recruited at different times, the study reference point was considered to be V_0 (the visit at the study end if no CHF, or the visit at the time of onset of CHF if CHF developed). V_{-1} was defined as the examination immediately prior to V_0. Thus, while all dogs were asymptomatic at V_{-1}, 30 (46%) dogs eventually developed CHF at V_0 and 35 (54%) dogs did not develop CHF. Median time between V_0 and V_{-1} for the 65 dogs was 137 days (89—183 days). At V_{-1}, the median murmur grade of the cohort was 4/6

Table 2 Univariate analysis of physical examination, echocardiographic, radiographic, and NT-proBNP parameters associated with future development of congestive heart failure in the derivation cohort.

Variable	OR (95% CI)	Coefficient	*P*-value
Gender (Female)	1.28 (0.53—3.09)	0.25	0.58
Age	1.14 (0.96—1.36)	0.13	0.14
Body weight	0.98 (0.94—1.03)	−0.02	0.46
Murmur grade ≥5	3.45 (1.56—7.62)	1.24	0.002
HR	1.11 (1.04—1.18)	0.10	0.002
VHS	5.87 (2.74—12.60)	1.78	<0.0001
LVIDd:Ao	203.9 (12.0—3455)	5.31	<0.0001
LVIDs:Ao	5.99 (1.22—29.3)	1.79	0.009
LA:Ao	2766.1 (60.8—125765)	7.92	<0.0001
TR velocity	3.16 (1.36—7.31)	1.15	0.007
NT-proBNP	1.00 (1.001—1.003)	0.0021	<0.0001

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(1–6/6). The median heart rate was 120 bpm (105–138 bpm). Baseline radiographic and echocardiographic data at V_{-1} were as follows: median VHS, 11.5 (10.75–12.0); LVIDd:Ao, 2.36 (2.16–2.86), LVIDs:Ao, 1.30 (1.12–1.53); and LA:Ao, 1.95 (1.83–2.10). Tricuspid regurgitation was present in 47 dogs (72%) and the median regurgitation velocity was 2.94 m/s (2.62–3.26 m/s). The median NT-proBNP concentration was 2013 pmol/L (1294–3001 pmol/L). The previously identified derivation regression equation, utilizing the variables NT-proBNP and LA:Ao at V_{-1}, was applied to the prospective cohort. Receiver operating characteristic analysis revealed an AUC of 0.737 (95% CI, 0.607–0.842), and a sensitivity and specificity to predict CHF of 88.9% and 57.6% respectively, at a cutoff value of 0.475. Overall accuracy of prediction (i.e., ability to correctly predict presence or absence of CHF at or prior to the next visit) was 69.2%. The risk of CHF in dogs <0.475 was 22.2% versus 63.2% in dogs >0.475 ($P = 0.001$), which resulted in a relative risk of CHF in dogs >0.475 of 2.84 (Fig. 2).

To identify other predictive variables in the validation cohort, logistic regression analysis was performed using data from V_{-1}. On univariate analysis, factors associated with future development of CHF included age, murmur grade ≥5, VHS, LA:Ao, LVIDd:Ao, LVIDs:Ao, and NT-proBNP (Table 3). The OR associated with a change in NT-proBNP of 250 pmol/L and 750 pmol/L, were 1.23 (95% CI, 1.04–1.45; $P = 0.014$) and 1.37 (95% CI, 1.02–1.85; $P = 0.014$) respectively. On multivariate analysis, significant independent risk factors associated with development of CHF at or prior to the next visit included NT-proBNP>1500 pmol/L (OR, 5.76; 95% CI, 1.37–24.28; $P = 0.017$) and LVIDd:Ao >3.0 (OR, 6.11; 95% CI, 1.09–34.05; $P = 0.039$). Additional analysis was performed under an assumption that echocardiographic evaluation would not be available at time of examination. After all echocardiographic-derived variables were removed from the multivariate model, NT-proBNP>1500 pmol/L (OR, 9.42; 95% CI, 1.74–51.11; $P = 0.009$) and VHS >12 (OR, 15.84; 95% CI, 2.43–103.43; $P = 0.004$) were found to be significant independent risk factors. Thus, in both the derivation and validation cohort, heart size and NT-proBNP concentration were significantly and independently associated with risk of developing CHF for dogs with asymptomatic DMVD.

Of the dogs that received 3 or more examinations ($n = 34$), logistic regression was used to assess the difference in variables between V_{-2} and V_{-1}. Univariate analysis showed that change in LVIDd:Ao (OR, 12.0; 95% CI, 1.01–142.1; $P = 0.049$) and LA:Ao (OR, 24.0; 95% CI, 1.03–561.2; $P = 0.048$) were significant; however the confidence intervals for these variables was extremely wide. Multivariate analysis did not detect a statistically significant difference of variables between V_{-2} and V_{-1}. The median time between V_{-2} and V_{-1} was 144 days (91–184 days) and between V_{-2} and V_0 was 293 days (208–364 days).

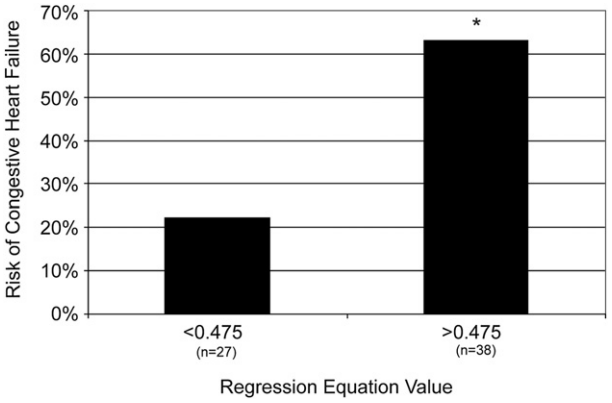

Figure 2 Risk of developing congestive heart failure in 65 dogs with chronic degenerative mitral valve disease based on a predictive regression equation that includes left atrial to aortic root diameter ratio (LA:Ao) and N-terminal B-type natriuretic peptide concentration (NT-proBNP). See text for regression equation. *$P = 0.001$.

Discussion

Canine DMVD is a common and generally progressive degenerative disorder. Assessing the risk for future morbidity and mortality is highly relevant, since some dogs develop heart failure while other affected dogs remain asymptomatic.[2] In this study, we identified four risk factors (LA:Ao, NT-proBNP, LVIDd:Ao and VHS) that placed affected but asymptomatic dogs at significant risk for CHF. Previously, NT-proBNP, normalized LVIDd,[17] and LA:Ao[2] were shown to predict all-cardiac mortality in dogs with DMVD. Given that life expectancy is relatively short once CHF occurs,[2] our results suggest that NT-proBNP and measures of left ventricular and atrial size can help predict risk for mortality.

In humans, NT-proBNP testing is viewed as part of a multi-factorial risk profile that includes established risk parameters such as hyponatremia, decreasing ejection fraction, widened electrocardiographic QRS complex, chronic hypotension, and renal insufficiency.[22] While clinical guidelines

Table 3 Univariate analysis of physical examination, echocardiographic, radiographic, and NT-proBNP parameters associated with future development of congestive heart failure in the validation cohort.

Variable	OR (95% CI)	Coefficient	*P*-value
Gender (Female)	0.76 (0.28–2.04	−0.54	0.59
Age	0.77 (0.61–0.97)	−2.20	0.028
Body weight	0.96 (0.86–1.05)	−0.89	0.37
Murmur grade ≥5	3.77 (1.34–10.6)	2.52	0.012
HR	1.01 (0.99–1.03)	1.34	0.18
VHS	2.53 (1.27–5.06)	2.63	0.008
LVIDd:Ao	11.6 (2.74–49.8)	3.32	0.001
LVIDs:Ao	15.6 (2.22–109.6)	2.76	0.006
LA:Ao	8.49 (1.61–44.6)	2.53	0.012
TR velocity	1.34 (0.54–3.38)	0.64	0.52
NT-proBNP (V_{-1})	1.00 (1.0001–1.0005)	2.45	0.014
ΔNT-proBNP (V_{-1}-V_{-2})	1.00 (0.99–1.00)	5.5×10^{-5}	0.87

discourage the use of any single test to assess future risk, NT-proBNP testing is nevertheless regarded as a useful test when combined with clinical assessment in selected patients.[23] Several studies have shown potential value of NT-proBNP for assessing heart disease in the dog. NT-proBNP was correlated with echocardiographic measurement of mitral regurgitant jet size and left ventricular and left atrial dimensions in dogs with asymptomatic DMVD.[14] A prospective survival study of 72 dogs with asymptomatic DMVD reported that 10 dogs that developed CHF in the subsequent 12 months had significantly higher NT-proBNP compared to dogs that remained compensated.[18] Two studies[15,16] have reported that VHS and echocardiographic left heart size increased most rapidly in the last time interval (typically 6–12 months) prior to the onset of CHF. In 23 of 24 dogs, the rate of change in VHS was greatest in the time interval immediately preceding onset of CHF, and in all dogs the highest VHS value was found at time of CHF.[15] These 2 studies were performed retrospectively and the current study expands on these findings by use of a prospective longitudinal study design and incorporation of variables from multiple diagnostic modalities. When mimicking clinical situations wherein echocardiography is not available, our data show that risk stratification could still be accomplished by evaluating VHS and NT-proBNP concentration.

Blood NT-proBNP concentration is an independent risk factor for morbidity and mortality in humans with DMVD. Specifically, NT-proBNP concentration increases with symptoms and severity of valvular disease.[6] In 124 human patients with DMVD, BNP was predictive of death or heart failure,[3] and in 87 human patients without symptoms, elevated NT-proBNP was highly predictive (ROC AUC of 0.84) of development of CHF symptoms.[4] Incorporation of BNP evaluation into the clinical work-up of humans with DMVD is recommended[24] based on the fact that the rate of 4-year CHF-free survival was 99% in patients in the lowest quartile of BNP values vs. only 29% in patients in the highest quartile.[8] Moreover, multivariate analysis revealed that BNP, along with LVIDd and effective regurgitant orifice area, was a significant predictor of onset of CHF or death.[8] Lastly, in 144 human patients with asymptomatic DMVD, NT-proBNP predicted first onset of symptoms with an accuracy of 76%,[25] similar to the findings in our study.

Incorporation of both a derivation and validation cohort in clinical study design assists in development of predictive clinical models,[26,27] and a previous study investigating the clinical utility of BNP in humans with asymptomatic DMVD[8] reports close relationship between the findings from the derivation and validation cohorts. The purpose of the derivation cohort is to construct a categorical model that is then prospectively tested on a separate population. This method provides a better assessment of the model's predictive ability, as accuracy is almost always overestimated in the derivation cohort compared to performance in the validation cohort.[28] In our study, while the derivation and validation cohorts were not identically recruited, multivariate analysis of the derivation cohort identified echocardiographic left atrial size and NT-proBNP as the two variables with the strongest correlation with CHF. Additionally, when the derivation equation was applied to the prospective cohort, future onset of CHF was correctly predicted in 69.2% of dogs.

The present study has several important limitations. The interval between visits was not standardized and this precluded the use of time-to-

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event statistical methods such as Kaplan—Meier and Cox proportional hazard analysis. Further studies using standardized recheck intervals and longer follow-up times would be informative. There was a relatively small number of dogs with more than two visits; this likely limited our ability to detect significant relationships between the rate of change of candidate variables and risk of CHF. The upper reported limit of the NT-proBNP assay is 3000 pmol/L, and given that this value was recorded in more than half of the dogs who developed CHF, increasing the upper detection range of the assay would likely provide additional prognostic information. The weekly variability of NT-proBNP in healthy dogs has been reported to be as high as 500 pmol/L,[29] and variability in dogs with DMVD is unknown. Renal function can influence NT-proBNP concentration[30] and we did not attempt to account or adjust for this parameter in our patient cohort. The echocardiographic information obtained in this study involved only basic measurements of heart size. Other studies examining Doppler-derived indices, such as the ratio of maximal mitral E wave velocity to isovolumic relaxation time, reported significant differences between dogs with and without CHF.[31] Further studies assessing these variables are needed, but measurement of many Doppler parameters requires operator expertise not typically found outside of a referral setting, thus limiting the clinical utility in general practice. Lastly, risk stratification is but one step towards better patient outcome. Once identified, high-risk patients should undergo intervention(s) to mitigate risk and improve outcome. As such, further studies are required to evaluate either specific medical therapy protocols or defined vigilance programs that could delay or prevent onset of CHF in high-risk patients.

Conclusions

Echocardiographic and radiographic measures of heart size, including LA:Ao, LVIDd, and VHS, as well as plasma NT-proBNP concentration independently estimate risk of first-onset of CHF in dogs with DMVD. These parameters can contribute to the management of dogs with DMVD.

Conflict of interest

This study was funded by IDEXX Laboratories Inc., Westbrook, ME. Drs. Oyama, Rush, Fox, Gordon, and Stepien serve on a veterinary advisory board for IDEXX Laboratories. The sponsor did not participate in the study design, data collection, analysis, or reporting of results.

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