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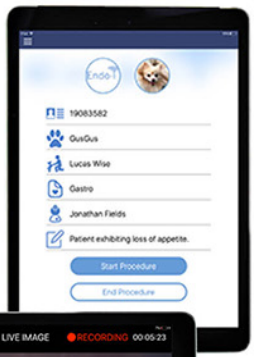

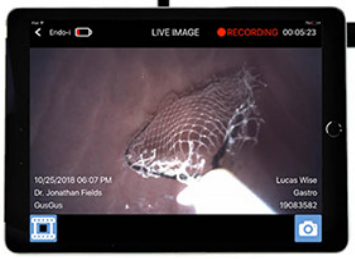

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Prospective Evaluation of NT-proBNP Assay to Detect Occult Dilated Cardiomyopathy and Predict Survival in Doberman Pinschers

G.E. Singletary, N.A. Morris, M. Lynne O'Sullivan, S.G. Gordon, and M.A. Oyama

Background: Occult (asymptomatic) dilated cardiomyopathy (ODCM) is highly prevalent in Doberman Pinschers.

Hypothesis/Objectives: Assess ability of NT-proBNP assay to detect ODCM and predict death.

Animals: 155 asymptomatic Dobermans presenting for ODCM screening.

Methods: Echocardiography, 24-hour Holter, and NT-proBNP assay were performed prospectively. Diagnosis was based on increased left ventricular end-systolic dimension, >50 ventricular premature complexes (VPCs), or both on Holter. Utility was evaluated using receiver-operating characteristic curves. Effect of age, weight, sex, disease status, VPCs, and NT-proBNP on survival was analyzed using Kaplan-Meier and Cox-proportional hazard analysis.

Results: Seventy-three (47.1%) Dobermans were diagnosed with ODCM, including 31, 17, and 25 that met Holter, echocardiographic, or both criteria, respectively. Sensitivity of NT-proBNP > 457 pmol/L to detect these groups was 45.2, 76.5, and 96.0%, respectively. Combination of NT-proBNP and Holter to detect ODCM yielded sensitivity of 94.5%, specificity of 87.8%, and accuracy of 91.0%. Follow-up data were available for 78 Dobermans. The median survival time of Dobermans with > 50 VPCs (469 days), NT-proBNP > 900 pmol/L (284 days), or ODCM (474 days) was significantly ($P < .0001$) shorter than those with < 50 VPCs (1743 days), NT-proBNP < 900 pmol/L (1743 days), or without disease (1743 days). NT-proBNP concentration and disease status were independently predictive of all-cause mortality.

Conclusions and Clinical Importance: The combination of NT-proBNP assay and Holter detected ODCM with high accuracy. NT-proBNP and disease status were independently associated with survival. NT-proBNP assay identified Dobermans with high probability of increased LVIDs consistent with ODCM, and can facilitate pursuit of confirmatory diagnostic testing, such as echocardiography, in suspected Dobermans.

Key words: Blood tests; BNP; Diagnostics; Heart disease; Natriuretic peptides.

Dilated cardiomyopathy (DCM) is a common cardiac disease with a lifetime incidence ranging from 45 to 62% in Doberman pinschers in the United States and Canada[1–3] and 58.2% in Europe.[4] DCM in the Doberman progresses through 3 distinct disease stages.[5] Stage I includes Dobermans that are asymptomatic and have no detectable morphologic or electrical abnormalities by conventional testing. Stage II, or the occult stage, involves the development of morphologic, electrical abnormalities, or both in the absence of any related clinical signs. Dogs with occult dilated cardiomyopathy (ODCM) can remain asymptomatic for years, but many ultimately progress to Stage III, during which syncope or clinical signs of heart failure are present and long-term survival is poor.[6] Diagnosis of ODCM currently involves either detection of ventricular arrhythmias on ECG or 24-hour ambulatory ECG recording (Holter), detection of left ventricular systolic dysfunction on echocardiographic examination, or both.[5] Most of these diagnostic tests are relatively expensive and typically require referral to a specialty practice with equipment and trained personnel capable of accurate assessment. Because of the high incidence of ODCM with increasing age,[5] yearly screening is recommended and incurs cumulative financial cost and owner commitment over the course of the dog's lifespan.

Dogs in both Stage II and III demonstrate increased circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations, presumably caused by increased atrial and ventricular wall stress.[7,8] The diuretic and vasodilatory effects of the natriuretic peptides serve as a counterbalance to the renin-angiotensin-aldosterone system.[9] In dogs, NT-proBNP is

Abbreviations:

DCM	dilated cardiomyopathy
E-ODCM	echocardiographic criteria for ODCM
H&E-ODCM	Holter and echocardiographic criteria for ODCM
H-ODCM	Holter criteria for ODCM
LVIDd	left ventricular end-diastolic dimension
LVIDs	left ventricular end-systolic dimension
NT-proBNP	N-terminal pro-B-type natriuretic peptide
ODCM	occult dilated cardiomyopathy
VPCs	ventricular premature complexes

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Preliminary results were presented at the 2009 ACVIM Forum and Canadian Veterinary Medical Association Convention, Montreal, Quebec, Canada.

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correlated with heart size and systolic function,[8] suggesting that natriuretic peptide concentrations can be used to detect animals with early disease. Dobermans with ODCM have plasma NT-proBNP concentrations that were significantly increased as compared with healthy dogs.[7] In addition, Dobermans with decreased ventricular systolic function have greater NT-proBNP concentration than Dobermans with only ventricular arrhythmias.[7]

Early detection of ODCM could enhance owner vigilance, alter breeding programs, and trigger therapeutic interventions. Blood-based testing represents a relatively inexpensive, easily performed, and widely available screening method that could aid in counseling owners regarding the likely value of further examination, such as echocardiography. The purpose of this study was to determine the ability of NT-proBNP to detect ODCM in Dobermans undergoing screening with Holter and echocardiographic examination, and to evaluate the ability of NT-proBNP to predict survival.

Materials and Methods

Doberman Pinschers that presented for ODCM screening to Mass Veterinary Cardiology Services (MVCS, West Springfield, MA) or the veterinary teaching hospitals of the University of Guelph (Guelph, Ontario), Texas A&M University (TAMU, College Station, TX), or the University of Pennsylvania (Philadelphia, PA) from 2007 and 2009 were eligible for inclusion. All dogs received routine 2D and M-mode echocardiograms[a] performed by either a board-certified cardiologist or a cardiology resident under direct supervision by a board-certified cardiologist. Left ventricular internal dimension in end-diastole (LVIDd) and end-systole (LVIDs) was obtained from 2D or M-mode echocardiographic images from either the right parasternal short or long-axis views and averaged over a minimum of 3 heart beats. Ventricular dimensions in both diastole (LVIDdN) and systole (LVIDsN) were normalized to body weight. At time of echocardiography, approximately 2 mL of blood was drawn into plain EDTA-tubes, centrifuged, and the resultant plasma was either frozen at −80°C until batch analysis or sent immediately after collection to the reference laboratory via overnight mail for NT-proBNP testing using a commercially available assay[b] Holter[c] examination was performed. To be included, at least 20 hours of analyzable recording was required. ODCM was diagnosed based on LVIDs greater than 38.8, 39.5, 40.2, 40.9, 41.6, 42.3, and 43.0 mm in dogs weighing up to 25, 30, 35, 40, 45, 50, and 55 kg, respectively, the presence of > 50 VPCs, or both during Holter.[5]

Statistical Analysis

Descriptive data was tabulated and reported as median (interquartile range, IQR) values. NT-proBNP assay results < 50 pmol/L or > 3000 pmol/L were coded as 49 pmol/L and 3001 pmol/L, respectively. Comparison of baseline variables between groups was performed using Mann-Whitney or chi-square tests. Receiver-operating characteristic curve and Fagan nomogram[10] analysis were used to determine the sensitivity and specificity, positive and negative predictive values, and positive and negative likelihood ratios of NT-proBNP assay to detect ODCM. Accuracy of the NT-proBNP assay was calculated as the percentage of true positive and true negative results out of the number of tests performed. After inclusion into the study, subsequent recheck examinations and telephone surveys collected data regarding ongoing diagnosis (healthy versus ODCM) and survival. If Dobermans were reported dead, the investigator determined the cause of death using review of medical records, interview of the owner, or both. Recheck examinations were performed at the clinician's discretion and neither the scheduling nor the diagnostic procedures at recheck examinations were standardized. Kaplan-Meier survival curve analysis and Wilcoxon log-rank tests were used to compare median survival times based on age, sex, body weight, VPCs, initial diagnosis, and NT-proBNP concentration. Dogs alive at the time of last follow-up were right censored. The effect of risk factors on survival was assessed using Cox–proportional hazard analysis. Statistical significance of all tests was defined as $P < .05$.

Results

One-hundred and fifty-five Dobermans were examined (MVCS, 83; Guelph, 40; TAMU, 17; Penn, 15). Of these, 73/155 (47.1%) fulfilled the criteria for ODCM and 82/155 (52.9%) were diagnosed as healthy (Table 1). Of the 73 Dobermans diagnosed with ODCM, 31/73 (42.5%) were diagnosed based on Holter criteria alone (H-ODCM), 17/73 (23.3%) by echocardiographic criteria alone (E-ODCM), and 25/73 (34.2%) fulfilled both criteria (H&E-ODCM) (Fig 1). Receiver-operating characteristic analysis of NT-proBNP concentrations to detect the 73 Dobermans with ODCM resulted in an area under the curve of 0.801 and a NT-proBNP cut-off of 457 pmol/L (Table 2). The sensitivity (69.9%) of NT-proBNP > 457 pmol/L to detect ODCM was relatively low attributable to the poor ability of NT-proBNP to detect H-ODCM. Median NT-proBNP in H-ODCM dogs was significantly lower than in E-ODCM or H&E-ODCM (H-ODCM, 324 [IQR, 231–701] pmol/L; E-ODCM, 681 [400–1471] pmol/L; H&E-ODCM, 1143 [748–2293] pmol/L; $P<=.0001$). Within the H-ODCM group, only 14/31 (45.2%) had NT-proBNP > 457 pmol/L. The sensitiv-

Table 1. Descriptive data of 155 Dobermans screened for occult dilated cardiomyopathy (ODCM). Values are presented as median (IQR).

	Healthy	ODCM	*P*
N	82	73	
Sex	52F/30M	23F/50M	<.0001
Age	6.0 (5.0–7.5)	6.7 (5.8–7.9)	.038
Weight (kg)	32.7 (29.2–38.4)	36.4 (32.5–40.0)	.001
LVIDd (cm)	4.26 (3.99–4.60)	4.94 (4.58–5.29)	<.0001
LVIDdN	1.52 (1.43–1.63)	1.74 (1.61–1.85)	<.0001
LVIDs (cm)	2.91 (2.60–3.14)	4.10 (3.50–4.50)	<.0001
LVIDsN	1.06 (0.94–1.14)	1.45 (1.22–1.55)	<.0001
VPCs/24 h	1 (0–9)	204 (56–846)	<.0001
NT-proBNP (pmol/L)	235 (164–430)	688 (327–1186)	<.0001

LVIDd, left ventricular dimension at end-diastole; LVIDdN, normalized left ventricular dimension at end-diastole; LVIDs, left ventricular dimension at end-systole; LVIDsN, normalized left ventricular dimension at end-systole; VPCs, ventricular premature complexes; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

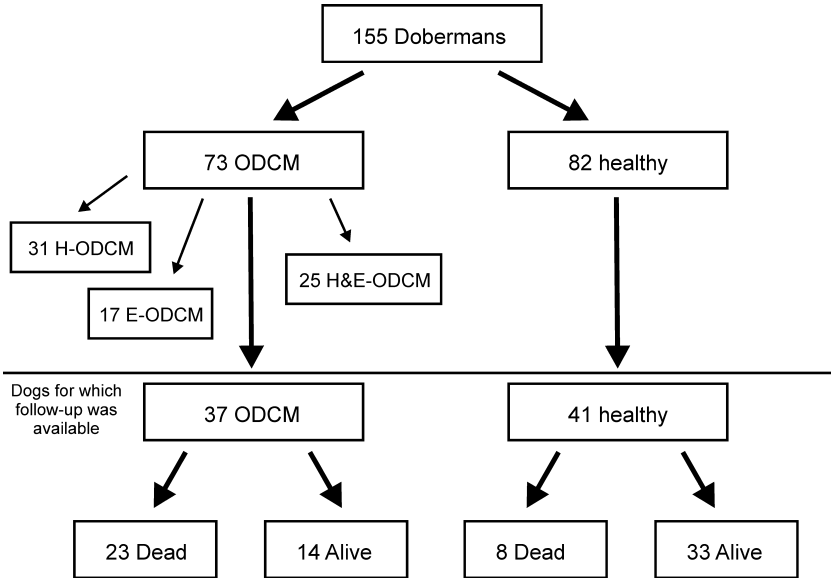

Fig 1. Flow diagram displaying initial diagnosis, follow-up, and outcome in 155 Dobermans. See text for abbreviations and details.

Table 2. Results of receiver-operating characteristic curve analysis and diagnostic utility of N-terminal pro-B-type natriuretic peptide (NT-proBNP) assay and Holter for the detection of occult dilated cardiomyopathy in 155 Dobermans. NT-proBNP concentration is listed as pmol/L.

Criteria	Se	Sp	PPV	NPV	LR+	LR−	Accuracy
NT-proBNP > 457	69.9	80.5	76.1	75.0	3.58	0.370	75.5
NT-proBNP > 900	32.9	93.9	82.8	61.1	5.39	0.710	65.2
Holter, NT-proBNP, or both > 457	94.5	87.8	87.3	94.7	7.75	0.062	91.0
Holter, NT-proBNP, or both > 900	84.9	95.1	93.9	87.6	17.41	0.158	90.3

NT-proBNP, N-terminal pro-B-type natriuretic peptide; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio.

ity of NT-proBNP > 457 pmol/L to detect E-ODCM or H&E-ODCM was much greater (E-ODCM, 13/17 [76.5%]; H&E-ODCM, 24/25 [96.0%]). The combined diagnostic criteria of either NT-proBNP > 457 pmol/L, an abnormal Holter had high sensitivity (94.5%), specificity (87.8%), and accuracy (91.0%), or both for detection of ODCM (Table 2). The addition of NT-proBNP assay to Holter recording as a diagnostic test improved sensitivity of detection from 56/73 (76.7%) Dobermans to 69/73 (94.5%) Dobermans.

Follow-up data was available for 78 Dobermans, including 41/78 (52.6%) healthy Dobermans and 37/78 (47.4%) ODCM Dobermans as diagnosed at time of initial examination. The median follow-up time was 506 days (range, 35–1815 days), during which time 31/78 (39.7%) Dobermans died (healthy, 8/41 [19.5%]; occult 23/37 [62.2%]) and 47/78 (60.3%) were still alive (healthy, 33/41 [80.5%]; occult, 14/37 [37.8%]) (Fig 1). Nine of 41 (22.0%) Dobermans originally diagnosed as healthy were subsequently diagnosed with either ODCM or overt DCM. Of the 8 Dobermans that were initially diagnosed as healthy, but died during follow-up, 3/8 (37.5%) died suddenly, 3/8 (37.5%) were euthanized because of noncardiac disease, and 2/8 (25.0%) were euthanized because of congestive heart failure. Of the 23 Dobermans originally diagnosed with ODCM that died during follow-up, 9/23 (39.1%) died or were euthanized because of heart failure or cardiac complications, 8/23 (34.8%) died suddenly, and 6/23 (26.1%) were euthanized for noncardiac reasons. Kaplan-Meier survival analysis examined the effect of age, sex, body weight, number of VPCs, NT-proBNP concentration, and initial disease status (healthy versus ODCM) on survival, and of these parameters, only number of VPCs, NT-proBNP concentration, and disease status were significantly associated with survival (Table 3). The median survival time of Dobermans with > 50 VPCs on Holter was 469 days and was significantly ($P < .0001$) shorter than dogs with < 50 VPCs (1743 days) (Fig 2A). The median survival time of Dobermans with NT-proBNP > 900 pmol/L was 284 days and was significantly ($P < .0001$) shorter than Dobermans with NT-proBNP < 900 pmol/L (1743 days) (Fig 2B). The median survival time of Dobermans with ODCM was 474 days and was significantly ($P < .0001$) shorter than Dobermans diagnosed as healthy (1,743 days)

(Fig 2C). Cox-proportional hazard analysis was performed using VPCs (number per 24 hours), NT-proBNP (> or < 900 pmol/L), and disease status (healthy versus ODCM), and indicated that only NT-proBNP and disease status were independently predictive of survival (NT-proBNP > 900 pmol/L: exp(b) hazard ratio = 4.40 (95% CI, 1.98–9.80), P = 0.0003; disease status (occult DCM): exp(b) hazard ratio = 6.54 (95% CI, 2.50-17.14), P = 0.0001; overall model fit: chi-square, 38.8; $P < .0001$). NT-proBNP result remained an independent predictor if entered into the hazard model as a continuous rather than dichotomous variable (NT-proBNP concentration: exp(b) hazard ratio = 1.0011 (95% CI, 1.0006–1.0016), P = 0.0001; disease status (occult DCM): exp(b) hazard ratio = 5.19 (95% CI, 1.93–13.98), P = 0.0012; overall model fit: chi-square, 41.0; $P < .0001$).

Table 3. Results of Kaplan-Meier survival analysis and Wilcoxon log-rank test to estimate the hazard for all-cause mortality during the follow-up period based on body weight, age, sex, ventricular premature complexes (VPCs), initial diagnosis, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration in 78 Dobermans.

Variable	Chi-Square	*P*	Hazard Ratio (95% CI)
Body weight (>35.1 kg)	1.04	.31	1.44 (0.71–2.92)
Age (>6.5 years)	2.18	.14	1.81 (0.80–4.10)
Sex (Male)	1.59	.21	1.55 (0.76–3.17)
VPCs (>50/24 h)	25.9	<.0001	5.29 (2.36–11.8)
Disease status (occult)	28.8	<.0001	6.36 (2.97–13.6)
NT-proBNP (>900 pmol/L)	35.5	<.0001	6.55 (1.89–22.7)

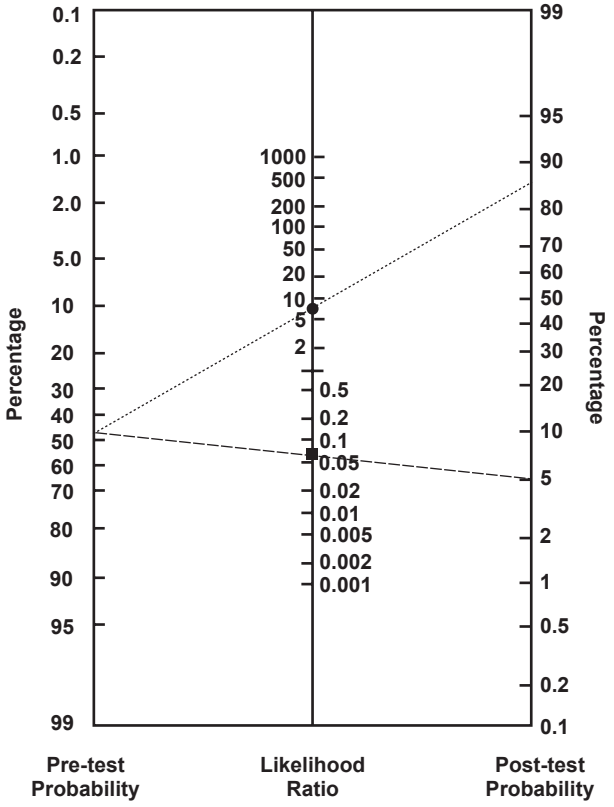

Fig 2. Kaplan-Meier survival curves comparing survival of Dobermans with (A) >50 (n = 47) or < 50 (n = 31) ventricular premature complexes (VPCs) on Holter, (B) plasma NT-proBNP concentration > 900 (n = 14) or < 900 (n = 64) pmol/L, and (C) with (n = 37) and without (n = 41) occult dilated cardiomyopathy at time of initial examination.

Discussion

The current study demonstrates that NT-proBNP assay, when performed in conjunction with Holter, is highly sensitive and specific for detecting ODCM in Dobermans. The presence of > 50 VPCs during Holter, an increased NT-proBNP concentration, or both indicated a > 7-fold likelihood or 87.3% chance of ODCM. Conversely, in the absence of these criteria the likelihood was approximately 16-fold less, equal to only a 5.3% chance of ODCM. The current results are in close agreement with a previous report[7] indicating that NT-proBNP could distinguish Dobermans with Stage II or Stage III DCM from healthy Dobermans, and that the diagnostic utility of NT-proBNP assay was higher in dogs with echocardiographic abnormalities compared with those with only Holter recording abnormalities. Specifically, NT-proBNP > 400 pmol/L detected echocardiographic abnormalities with a sensitivity of 90.0% and specificity of 75.0%, whereas sensitivity and specificity to detect Dobermans with Holter abnormalities were only 69.9 and 75.3%, respectively.[7] The current study expands on these findings by reporting diagnostic utility in Dobermans only with Stage II (ODCM) disease and from a North American cohort with different ancestry than was previously reported.

Diagnostic tests used for detection of disease (ie, for screening) benefit from high sensitivity to minimize false negative results. Sensitivity and specificity are inversely related, such that changes in sensitivity affect specificity and vice versa. Thus, if the cut-off NT-proBNP concentration was decreased from 900 pmol/L, which has been reported as the upper reference limit for healthy animals,[11] to 457 pmol, sensitivity increased from 84.9 to 94.5% and specificity decreased from 95.1 to 87.8%. A previous study[12] using C-terminal BNP radioimmunoassay reported sensitivity of 92% and specificity of 62% for detection of ODCM. Thus, a detection strategy using NT-proBNP assay is better suited for clinical use versus C-BNP by providing superior specificity. This finding might be attributable to the purported greater stability of the NT-proBNP molecule as compared with C-terminal BNP or differences in measurement methodologies.

Interpretation of a diagnostic test's sensitivity and specificity is affected by disease prevalence, and clinical utility can be over- or underestimated if the study population differs from the real population. Likelihood ratios, which indicate how much more or less likely a patient is to have disease based on the given test result;

can be used to calculate the posttest risk of disease in a given individual. Nomogram-based systems[10,13] incorporate positive and negative likelihood ratios to determine the posttest probability of disease across a range of disease prevalence values (Fig 3). This method has been used to predict future congestive heart failure based on radiographic heart size in dogs with mitral valve disease.[14] Results of further studies that determine the specific prevalence of ODCM within well-defined subpopulations based on variables such as age, sex, geographic location, and lineage could be used with existing likelihood ratios to achieve the most accurate predictions of presence of disease.

The close correlation between NT-proBNP concentration and echocardiographic abnormalities in Dobermans with ODCM indicates neurohormonal activation in the early stages of the disease process. In the current study, morphologic evidence of ODCM relied on the finding of increased LVIDs, which is an early echocardiographic change in ODCM.[4] Such change has been previously shown to increase release of atrial natriuretic peptide.[15] The relationship between ventricular arrhythmias and natriuretic peptide release is less clear. Natriuretic peptide concentrations predict presence of ventricular arrhythmias and risk of sudden cardiac death independent of decreased cardiac ejection fraction in human meta-analysis.[16] In contrast, NT-proBNP assay had low sensitivity for detection of ODCM in the H-ODCM group. The reasons for this finding remain unclear, but might involve interday variability in arrhythmia severity, the relatively low number of ventricular arrhythmias present in any individual dog, and the fact that blood sampling for NT-proBNP assay was not performed simultaneously using Holter examination. Alternate biomarkers of cellular damage, electrical dysfunction, or arrhythmias, such as cardiac troponin, might be superior or complementary to NT-proBNP assay in detecting H-ODCM.[17,18]

NT-proBNP concentration was independently associated with all-cause mortality. Median survival time in Dobermans with increased NT-proBNP concentration was 6.1 times shorter than in Dobermans with lower concentrations. Dobermans with increased NT-proBNP concentration or with ODCM were 4.4 and 6.5 times more likely to die than Dobermans with normal NT-proBNP concentration or without evidence of ODCM at initial examination, respectively. These data suggest that activation of the natriuretic peptide system occurs both before and during detectable disease development and is this phenomenon is reflective of disease severity. These findings agree with data indicating that NT-proBNP concentration predicts cardiovascular morbidity and all-cause mortality in dogs with degenerative mitral valve disease.[19,20] NT-proBNP assay is predictive of mortality in humans with idiopathic DCM,[21,22] and patients with increased concentrations are 4.6 times more likely to die as compared with those with lesser values.[23]

DCM is defined as an idiopathic disorder in which "the heart muscle is structurally and functionally abnormal",[24] is characterized by "ventricular chamber

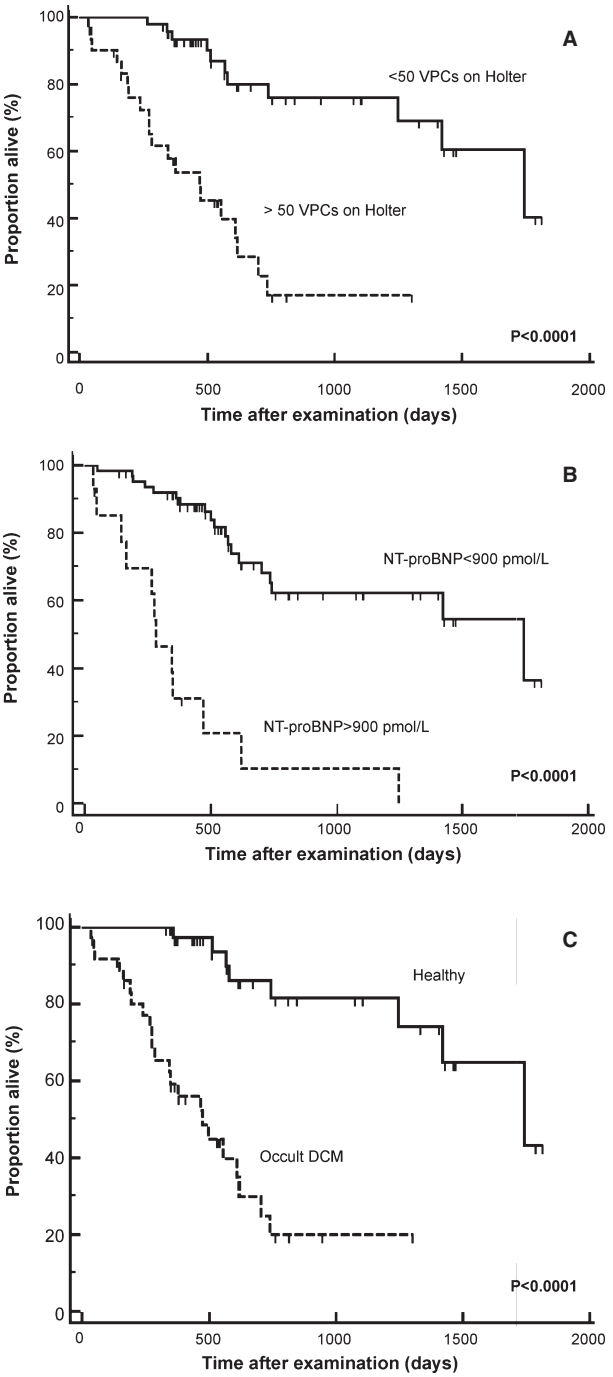

Fig 3. Nomogram illustrating the derivation of post-test probability of occult dilated cardiomyopathy (ODCM) in 155 Dobermans. The 1st column represents the pretest probability (ie, prevalence) of disease in the population being tested. The 2nd column represents the positive (circle) or negative (square) likelihood ratio of disease presence based on results of Holter and NT-proBNP assay. The 3rd column represents the posttest probability of having ODCM and is determined by drawing a line that connects the pretest probability and likelihood ratio. Examination of the nomogram system reveals that posttest probability is heavily influenced by the pretest prevalence of disease in the population being tested. (Nomogram adapted from Fagan[10]).

enlargement and systolic dysfunction",[25] and that "diagnosis [of DCM] is [usually] made using 2-dimensional echocardiography".[25] Thus, the authors of the current study emphasize that NT-proBNP assay is not a definitive diagnostic test for ODCM, and should not be regarded as a replacement for echocardiographic examination or Holter. Rather, NT-proBNP assay is a means to determine the likelihood of increased LVIDs and to better weigh the pros and cons of the financial cost and potential inconvenience of echocardiographic evaluation. Ultimately, decisions regarding diagnosis of ODCM are dependent on echocardiography and Holter, and in the case of breeding soundness, also on genetic testing. Moreover, a normal NT-proBNP concentration at a single time point does not exclude the possibility of future development of DCM. Thus, rescreening over the course of the dog's life is recommended.

There are several potential limitations to the current study. The study population presented itself to referral hospitals specifically for ODCM screening, and results of this study only are valid inasmuch as the study population reflects the real population. In the current study, the median age (6.0–6.7 years) and prevalence of disease (47.1%) of the study cohort generally agree with previous descriptions of ODCM in Dobermans.[5,26,27] Another potential limitation involves the NT-proBNP assay itself, which underwent revision by the manufacturer at or near the time of study commencement (A.B., personal communication), and again in 2010 with introduction of sample collection tubes containing a protease inhibitor. In the current study, all samples were collected and handled according to manufacturer guidelines that were current at the time of collection. Nevertheless, the NT-proBNP values described in this study might be different from those obtained using the most recent iteration of the assay or from NT-proBNP assays from other manufacturers. As such, additional investigation is needed to determine the comparability of results from various versions of the assay.

In conclusion, the combination of NT-proBNP assay and Holter detected ODCM in Dobermans with high accuracy. NT-proBNP was independently associated with survival. NT-proBNP assay and Holter can be used to identify Dobermans at high risk for ODCM and to facilitate the pursuit of confirmatory diagnostic testing, such as echocardiography, in suspected individuals.

Footnotes

[a] Sonos 7500, Philips Medical Systems, Andover, MA; Vivid7, GE Healthcare, Little Chalfont, UK; Cypress, Siemens Medical Solutions, Malvern, PA

[b] Canine CardioCare, Veterinary Diagnostics Institute, Irvine, CA; CardioPet NT-proBNP, IDEXX Laboratories Inc, Westbrook, ME

[c] Impresario, Pathfinder, SpaceLabs Healthcare, Issaquah, WA; RZ151, Rozinn Electronics, Glendale, NY

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Conflict of Interest: Authors disclose no conflict of interest.

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