The occurrence of preclinical dilated cardiomyopathy in the Weimaraner dog breed and the prognostic importance of cardiac markers

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Received June 26, 2024
Accepted December 12, 2024

Abstract

Dilated cardiomyopathy (DCM) is a major cause of morbidity and mortality in various dog breeds, being the second most common acquired cardiac disease in dogs. The most frequently affected breeds are Doberman Pinchers, Great Danes, Boxers, Irish Wolfhounds and others. We found out that the Weimaraner breed also suffers from this disease. Prospective dog screening may identify animals with DCM at Stage B. In the study, a total of 331 dogs of the Weimaraner breed were enrolled. Of the total number, 300 dogs were healthy. Seventeen dogs were diagnosed with preclinical DCM. The cut-off value for preclinical DCM of NTproBNP (N-terminal prohormone of brain natriuretic peptide) was 405 pmol/l, sensitivity was 73% and specificity was 72%. The cut-off value for preclinical DCM of troponin I was 0.04 ng/ml, sensitivity was 66% and specificity was 88%. This is the first study to evaluate the use of NTproBNP and cTnI as markers of preclinical DCM in Weimaraners. Setting the cut-off values for these parameters shows its clinical validity in detecting the disease, such as the possibility of using these tests in routine clinical practice.

Canine, DCM, CHF, cTnI, NTproBNP

Dilated cardiomyopathy (DCM) is the most common cardiac disease in large-breed dogs. A modified staging system for canine DCM could be clinically useful (Wess 2022). Stage A is characterized by no evidence of clinical signs of heart disease and a morphologically and electrically normal heart. At this stage, the dogs have a predisposition to develop DCM. Preclinical DCM or Stage B is described by evidence of morphologic or electrical lesions but without evidence of congestive heart failure (CHF). Stage B1 is the arrhythmogenic stage without cardiac enlargement, but includes ventricular premature complexes (VPCs). Stage B2 is typical for dogs with systolic dysfunction (which means left chamber enlargement) and at this stage, the dogs may or may not have arrhythmias. At Stage C the dogs have clinical signs of congestive heart failure. Stage D is the end-stage DCM and is refractory to standard therapy. The mentioned staging system is similar for myxomatous mitral valve disease (Keene et al. 2019), for feline cardiomyopathy (Luis Fuentes et al. 2020) and for humans, too (Hunt et al. 2001).

Cardiac troponins are sensitive and specific markers of myocardial injury. Troponin consists of 3 subunits (cTnI, cTnT, and cTnC) which function together as the molecular switch of cardiomyocyte contraction (Langhorn and Willesen 2016). In humans, the

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primary value of cTnI as a biomarker is to detect myocardial infarctions (Jishi et al. 2004). This protein is detectable in the blood 3–12 h after cardiac injury, peaks at 1–2 days, and dissipates by 5–10 days in humans (Eisenman 2006). Cardiac troponin concentrations can be measured in dogs, cats, horses, and its alterations can be seen in animals with a variety of diseases including gastric dilations and volvulus, babesiosis, blunt trauma, infarction, congestive heart failure, and hypertrophic cardiomyopathy (Spratt et al. 2005). Troponin I has 81.2 % sensitivity and 73.2% specificity in diagnosing occult DCM (Klüser et al. 2019).

Natriuretic peptides participate in the integrated control of renal and cardiovascular function (Wei et al. 1993). Investigations have demonstrated the existence of a family of structurally related peptides, the atrial (ANP), brain (BNP), and C-type natriuretic peptides (Yasue et al. 1989; Arbustini et al. 1990). The major stimulus for the release of BNP by the heart is an increase in intracardiac hydrostatic pressure (Luchner et al. 1998). The BNP increases natriuresis, urine production, and renal blood flow and decreases systemic vascular resistance (Goetze et al. 2005). In CHF, the plasma concentrations of ANP are increased in response to increased atrial stretch and increased heart rate, whereas circulating BNP increases primarily in response to ventricular dysfunction and dilation (Wei et al. 1993).

N-terminal prohormone of brain natriuretic peptide (NTproBNP) is a marker of myocardial injury too. Cardiac marker NTproBNP was higher in Dobermann Pinschers with DCM or in patients that developed DCM within 1.5 years. Sensitivity was 90% and specificity was 75% (Wess et al. 2011). This marker has a sensitivity of 90.4% to detect echocardiographic changes (Wess et al. 2011).

The aim of the study was to determine the ‘cut-off value’ for DCM at Stage B in the dogs of the Weimaraner breed.

Materials and Methods

Study design

This prospective study focused on Weimaraner dogs exclusively and was conducted at the Small Animal Clinic, University of Veterinary Sciences Brno (VetUni Brno), and the Slaný Veterinary Clinic. The dogs were examined unsedated upon the owner’s written consent. For a comprehensive haematological and biochemical analysis, blood samples were collected from the jugular vein. Analysis of indices such as total protein, albumin, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, glucose, Na, K, P, Cl, Ca, and Mg was conducted in clinical laboratories of the Small Animal Clinic (VetUni Brno) with Idexx Catalyst Dx Analyzer (biochemistry analyzer, Idexx Laboratories, Ins., Westbrook, Maine, USA) and Idexx ProCyte Analyzer (haematology analyzer, Idexx Laboratories, Kobe, Japan). Thyroid hormones (thyroxine and thyroid-stimulating hormone) and troponin I and NTproBNP were measured at the IDEXX laboratory (Hoofddorp, Netherlands).

Standard six-lead electrocardiography (ECG) was carried out using SEIVA EKG Praktik Veterinary (Prague, Czech Republic) and Eickemeyer PC-ECG (Tuttlingen, Deutschland). Following this, the patients displaying diagnostic arrhythmias on the ECG underwent subsequent Holter examinations. Echocardiographic evaluations were performed using the ALOKA 7 ultrasound with a 2.5–5 MHz phased array probe (Aloka CO., LTD, Tokyo, Japan) and the GE Vivid E95 with a 1.5–4.6 MHz phased array probe (GE Vingmed Ultrasound, Horten, Norway).

Echocardiography assessments were conducted with animals positioned in right and left lateral recumbency on a table featuring a ‘cutout’ section, and in some cases, the patients were examined in a standing position. The diagnostic approach for DCM followed the guidelines outlined by Dukes-McEwan et al. (2003), evaluating the left ventricular size, shape, and myocardial systolic function. Apart from the requirement for an abnormality in at least one of these criteria, the guide complements other relevant values obtained from echocardiography or electrocardiography.

To identify occult DCM, we employed a comprehensive approach using all parameters suggested by Dukes-McEwan et al. (2003) and incorporated Simpson’s method (Wess et al. 2017). In assessing early echocardiographic changes in Doberman Pinschers, Simpson’s method of discs (SMOD) was more sensitive than M-mode (Wess et al. 2010a). The left ventricle (LV) volume, determined by using SMOD, was measured in the right parasternal long-axis 4-chamber view and the left apical 4-chamber view, with measurements taken from both views and the larger volumes utilized.

Statistical analysis

Spearman correlation was performed using StatSoft, Inc. (2014) STATISTICA 12 (Tulsa Oklahoma, USA). Specificity, sensitivity and cut-off point of NTproBNP and troponin I for preclinical DCM (Stage B DCM) and DCM were calculated using the Receiver Operating Characteristic curves (ROC) using the software Epitools (https://epitools.ausvet.com.au/roccurves). Statistical significance was set at a level of $P \leq 0.05$.

Results

A total number of 331 Short-haired Weimaraners were enrolled in the study. Of these, 191 were females, of which one was spayed, and 140 were males, of which one was neutered. Out of the total of 331 dogs, 300 were found to be healthy, Stage B2 DCM was diagnosed in 17 patients, and the arrhythmogenic Stage B1 form of DCM was diagnosed in 4 dogs. Eleven of the 17 patients were males and six were females. The cut-off value for preclinical DCM for NTproBNP was 405 pmol/l with a sensitivity of 73% and a specificity of 72%. The cut-off value for preclinical DCM for troponin I was 0.04 ng/ml with a sensitivity of 66% and a specificity of 88%. The cut-off value for DCM for NTproBNP was 4,235 pmol/l, and both sensitivity and specificity were 100%. The cut-off value for DCM for troponin I was 0.14 ng/ml with a sensitivity of 100% and a specificity of 88% (Table 1, Figs 1–3).

Table 1. The cut-point sensitivity and specificity for troponin I and N-terminal prohormone of brain natriuretic peptide (NTproBNP) for preclinical dilated cardiomyopathy (DCM in stage B) and dilated cardiomyopathy.

	Healthy vs. pre-DCM	Pre-DCM vs. DCM
Troponin I		
Cut-point	0.04	0.14
Sensitivity	0.667	1.0
Specificity	0.882	0.857
NTproBNP		
Cut-point	405	4,235
Sensitivity	0.733	1.0
Specificity	0.722	1.0

Pre-DCM - preclinical dilated cardiomyopathy; DCM - dilated cardiomyopathy

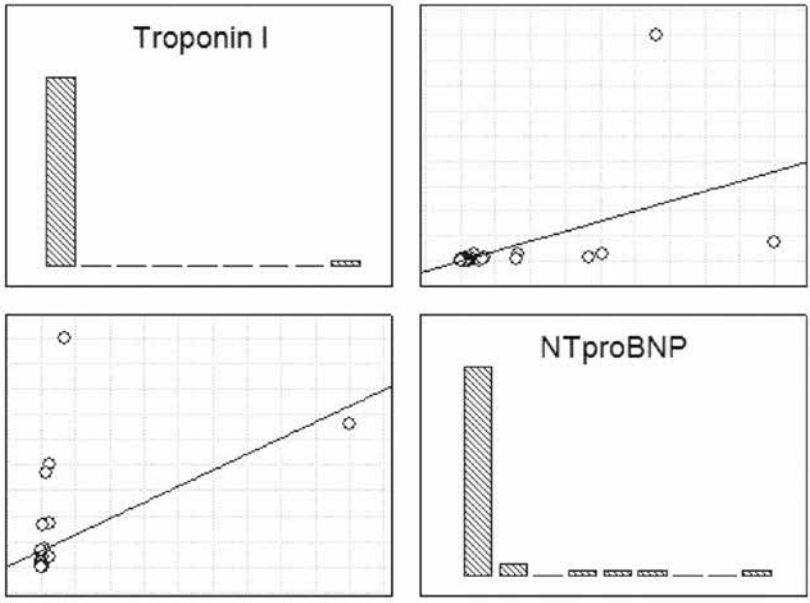

Fig. 1. Spearman correlation between troponin I and N-terminal prohormone of brain natriuretic peptide (NTproBNP) values

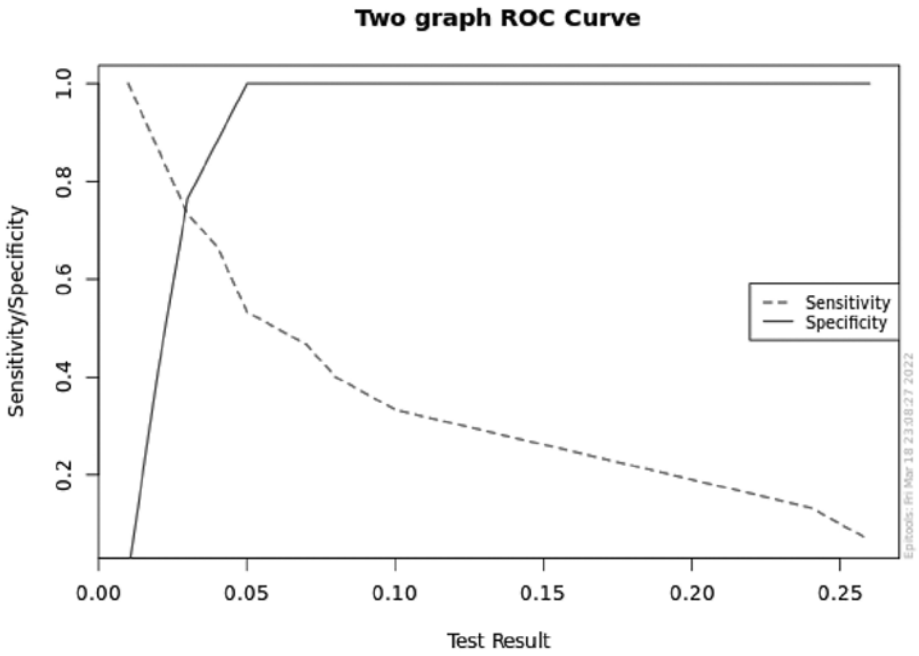

Fig. 2. Two-graph receiver operating characteristic (ROC) curves with sensitivity and specificity plotted against troponin for Weimaraner dogs.

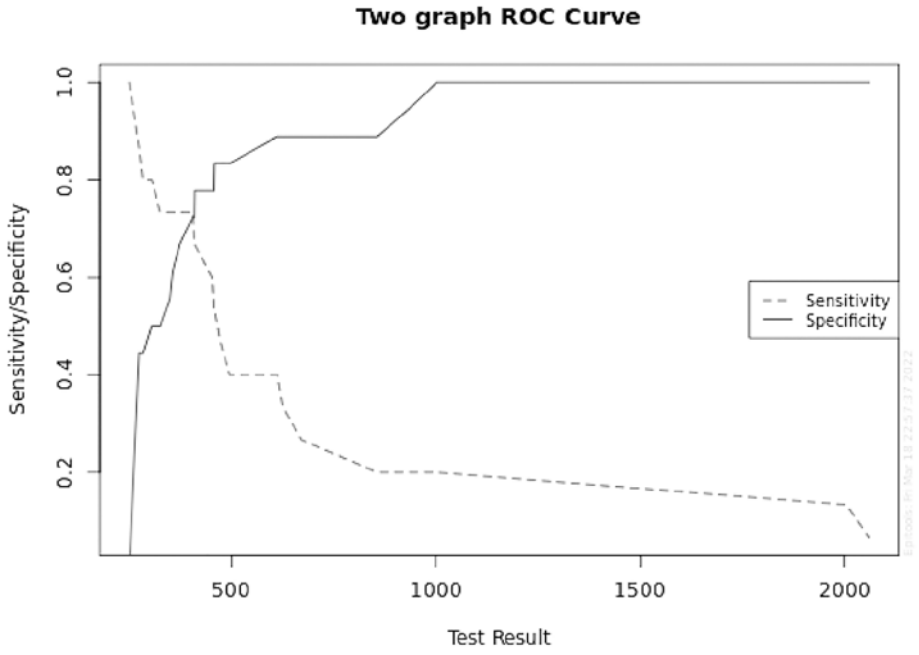

Fig. 3. Two-graph receiver operating characteristic (ROC) curves with sensitivity and specificity plotted against N-terminal prohormone of brain natriuretic peptide (NTproBNP) for Weimaraner dogs.

Discussion

Cardiac troponins are currently the most specific and sensitive indicators of myocardial cell damage. The troponin proteins form part of the contractile myofibrillar apparatus where they are responsible for regulating the interaction of actin and myosin in the control of muscle cell contraction. Following cardiac injury, troponins are released into the circulation from damaged myocytes (Spratt et al. 2005). In one study (Wess et al. 2010b) it was reported that troponin I was significantly elevated in Dobermans with DCM. Cardiac troponin I is high in dogs with cardiac disease and correlates with the heart size and survival. The elevation was not only detected in Dobermans with echocardiographic changes but also reported in dogs with VPCs. In this study, a total of 269 dogs were examined by physical examination, electrocardiography, and echocardiography, and the level of plasma TnI was measured (Oyama and Sisson 2004). One hundred seventy-six dogs out of 269 were healthy and median plasma cTnI was compared with cardiac disease: cardiomyopathy (CM), myxomatous mitral valve disease (MMVD), and subaortic stenosis (SAS). In dogs with CM and MMVD, the level of plasma TnI correlated with the left ventricle and left atrial size. In dogs with SAS, TnI plasma correlated with the thickness of the wall of the left ventricle (Oyama and Sisson 2004). Another study found a significant difference in serum TnI level in dogs with pericardial effusion compared to normal dogs, but TnI level was higher in dogs with pericardial effusion secondary to haemangiosarcoma compared to dogs with idiopathic pericardial effusion (Shaw et al. 2004). TnI has low sensitivity for the diagnosis of preclinical DCM, but in the study by Wess et al. (2010b), 23 out of 653 Dobermans were initially diagnosed as healthy based on echocardiography and Holter examinations. Subsequently, within 1.5 years they were diagnosed with DCM. The cut-off value of TnI at the initial examination was > 0.22 ng/ml (Wess et al. 2010b).

The best cut-off value for cTnI to predict DCM in Doberman Pinchers using a first-generation cTnI assay (Immulite assay) was 0.22 ng/ml (79.5% sensitivity and 84.4% specificity) (Wess et al. 2010b). A cut-off value of high sensitivity for cTnI assay (Advia Centaur TNI-Ultra assay) is with concentration > 0.113 ng/ml, which had a sensitivity of 81.2% and a specificity of 73.2% in identifying the presence of DCM (Klüser et al. 2019). Higher cut-off values of > 0.242 ng/ml cTnI increased the specificity to detect all DCM disease stages (Klüser et al. 2019) which is consistent with a previously conducted study (Wess et al. 2011). In our study, the cut-off value for cTnI concentration was 0.04 ng/ml for preclinical DCM and 0.14 ng/ml for clinical DCM. Concentrations of cTnI might be higher in Greyhounds and Boxers compared to other breeds (Baumwart et al. 2007; LaVecchio et al. 2009). This study shows that cTnI can be increased in dogs with noncardiac diseases such as gastric dilatation volvulus, babesiosis, kidney diseases, pulmonary hypertension and systemic inflammatory response syndrome. In our study, we include only clinically healthy dogs without any abnormalities in blood tests to eliminate the influence of cTnI by other diseases. The patients did not show any evidence of pulmonary hypertension on echocardiography. In the study of Spratt et al. (2005), there was no elevation of cTnI in patients with congenital heart abnormalities, which is in correlation with the study from human medicine in which it was found that pediatric patients have no elevations of cardiac troponin levels (Taggart et al. 1996).

The study of Gordon et al. (2016) evaluated 449 Doberman Pinchers and reported 100% sensitivity and 79% specificity to detect the characteristic echocardiographic morphologic changes of DCM with or without concurrent evidence of VPCs on a 3-min ECG for cTnI cut-off values of > 0.139. The best cut-off value for cTnI to predict DCM was 0.22 ng/ml (with a sensitivity of 79% and a specificity of 84.4%). In the study of Oyama and Sisson (2004), the median survival time of dogs with cTnI > 0.20 ng/ml was 112 days versus 357 days in dogs with cTnI < 0.20 ng/ml with cardiomyopathy.

However, due to low sensitivity and specificity, determination of troponin concentration does not replace echocardiography or Holter examination (Pérez et al. 2020).

The volume or pressure overload of the heart leads to an increase in NTproBNP concentration (Wess et al. 2011). The study of DeFrancesco et al. (2007) has found that the concentration of NT-proBNP is higher in dogs with heart disease and can be used to differentiate dyspnoea from cardiogenic or non-cardiogenic causes (DeFrancesco et al. 2007). In the study of Oyama et al. (2008), the serum NT-proBP concentration was significantly different between healthy control dogs and dogs with cardiac disease, between dogs with congestive heart failure and without congestive heart failure (Oyama et al. 2008). In the study by Wess et al. (2011) which included 328 Doberman Pinschers, plasma NT-proBNP concentration was significantly higher in Dobermans with DCM diagnosed by echocardiography only or by both echocardiography and a Holter, compared to healthy dogs. In this study, the best cut-off value for NT-proBNP for the prediction of echocardiographic abnormalities indicative of DCM was > 550 pmol/l (with a sensitivity of 78.6% and a specificity of 90.4%). The cut-off value of > 400 pmol/l increased the sensitivity up to 90.0% and the specificity decreased to 75% (Wess et al. 2011). In our study, the cut-off value of NTproBNP was 405 pmol/l with a sensitivity of 73% and a specificity of 72%, which is consistent with their results (Wess et al. 2011).

NTproBNP concentration can be affected by concurrent disease processes such as renal dysfunction, pulmonary hypertension, sepsis or systemic hypertension (Wess 2022). By thorough clinical and cardiology examination together with haematological and biochemical blood examinations that were conducted in our patients, we were able to exclude these diseases, and thus they should not affect the results of our study.

In another study by Singletary et al. (2012), Holter examinations with the determination of NTproBNP with the cut-off value of > 457 pmol/l had a sensitivity of 94.5% and a specificity of 87.8% in the detection of occult dilated cardiomyopathy (Singletary et al. 2012). NTproBNP concentration was the most accurate parameter for the detection of occult DCM (Wess et al. 2011). In another breed, the cut-off value of NTproBNP of > 900 pmol/l predicted cardiac enlargement but was not sensitive and specific for the diagnosis of Stage B DCM (Oyama et al. 2013). In our study, the cut-off values were 405 pmol/l for Stage B DCM and 4,235 pmol/l for clinical DCM. According to the study by Wess et al. (2017), the best cut-off value for the prediction of echocardiographic abnormalities indicative of DCM was > 550 pmol/l, but as the gold standard, it is still recommended to perform echocardiography together with Holter examination in Doberman Pinschers once every two years (Wess et al. 2017). The reference range of the NTproBNP and cTnI was only measured in Doberman Pinschers of preclinical DCM. Despite its reported usefulness, the NT-proBNP assay does not replace recommended diagnostic procedures such as echocardiographic examination where the sensitivity and specificity of detecting left ventricular dysfunction can be as high as 97% (Wess et al. 2011).

Our study is the first one to describe the reference ranges and cut-off values of NTproBNP and cTnI in Weimaraners. Examinations of these parameters might be very useful as a quick diagnostic test to rule out the presence of preclinical DCM in this breed. The authors are aware that only a small group of Weimaraners with Stage B DCM was eventually found in this study. Nevertheless, the obtained data are still valuable in setting a foundation for the use of NTproBNP and cTnI as markers of this disease in clinical practice.

Acknowledgements

This work was supported by funds from the grant agency IGA VFU Brno (FVL IGA 2020 – project no.117/2020/FVL) of the University of Veterinary Sciences Brno.

Partial results of the study were presented at the Conference of Internal Grant Agency VFU Brno on December 10, 2020.

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