Original Article

Diagnostic value of echocardiographic indices and cardiac biomarkers in dogs with chronic mitral valve insufficiency

Hyun-Seok Kim Sang-Il Suh Changbaig Hyun*

Abstract

Because all dogs having heart diseases are not in symptomatic heart failure stage, it is important to determine the stage of heart failure in dogs with heart diseases. Therefore, this study evaluated the diagnostic value of several echocardiographic parameters and cardiac biomarkers for differentiating dogs with heart disease from healthy dogs and dogs with symptomatic heart failure from dogs with asymptomatic heart failure. The study population consisted of 51 dogs having chronic mitral valvular insufficiency (CMVI) with varying degrees of heart failure and 18 healthy control dogs. Several echocardiographic parameters and cardiac biomarkers were evaluated to achieve the study aims. The study found that there were significant differences in indexed left atrial diameter (iLA), left atrial to aorta ratio (LA/Ao), left ventricular diastolic dimension to aorta ratio (LVIDd/Ao), transmitral E-peak (E-peak), septal E/Ea ratio (sE/Ea), parietal E/Ea ratio (pE/Ea) and N-terminal probrain natriuretic peptide (NT-proBNP) between the control dogs and the CMVI dogs ($P<0.05$), and also between the asymptomatic dogs and the symptomatic dogs ($P<0.05$). The cut-off values for indicating heart disease in this study population were iLA >11.9 mm, LA:Ao >1.32, LVIDd/Ao >1.91, E-peak >80 cm/sec, sE/Ea >7.0, pE/Ea >6.9, and NT-proBNP >980 pmol/L, while the cut-off values for indicating heart failure were iLA >12.7 mm, LA:Ao >1.58, LVIDd/Ao >2.08, E-peak >90 cm/sec, sE/Ea >9.0, pE/Ea >8.9, and NT-proBNP >1200 pmol/L. This study found that iLA, LA/Ao, E-peak, E/Ea and NT-proBNP were the most reliable and consistent markers for detecting heart disease and differentiating symptomatic heart failure dogs from asymptomatic dogs with CMVI.

Keywords: echocardiography, cardiac biomarker, heart failure, dog, mitral valve insufficiency

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Introduction

Chronic mitral valvular insufficiency (CMVI) is a degenerative valvular disease and is the most common heart disease in small dog breeds (Buchanan, 1999; Haggstrom et al., 2004; Suh et al., 2016). The common clinical consequences from CMVI are caused by mitral regurgitation (MR) and congestive heart failure (CHF) (Fox, 2012). Although the exact etiology has not yet been identified in dogs, degenerative valvular changes from aging and genetic involvement were proposed as the cause in a certain breed of dogs (Swenson et al., 1996; Olsen et al., 1999; Pedersen et al., 1999) and humans (Pomerance and Whitney, 1970; Enriquez-Sarano et al., 1994).

Diagnosis of CMVI is generally based on the onset of clinical signs along with diagnostic evidences from medical imaging studies including the transthoracic echocardiographic examination. Echocardiography is the most common and easiest diagnostic method for identifying mitral valvular lesions and evaluating the severity of CMVI (Pedersen et al., 1999; Hansson et al., 2002; Serres et al., 2006 and 2008; Bonagura and Schober, 2009; Terzo et al., 2009; de Madron et al., 2011; Nakamuraet al., 2014; Sargent et al., 2015). Common diagnostic features of CMVI include thickening of mitral leaflets, rupture of chordae tendinae, mitral valve prolapse to left atrium (LA), and abnormal excursion (i.e. decreased EF slope) and can also be detected in M-mode echocardiography (Pedersen et al., 1999; Terzo et al., 2009). Furthermore, echocardiography along with cardiac biomarker assays was found to be useful to predict the progression of CHF in dogs (Spratt et al., 2005; DeFrancesco et al., 2007; Serres et al., 2009; Moonarmart et al., 2010; Wolf et al., 2012). Known echocardiographic indices and cardiac biomarkers for predicting the progression of CHF are left atrial to aortic root ratio (LA/Ao), left ventricular diastolic dimension to aortic root ratio (LVIDd/Ao), transmitral E-peak velocity (E-peak), E-peak to Ea-peak ratio (E/Ea), regurgitation fraction of mitral valve into LA (MR fraction) and end diastolic volume index (EDVI), plasma N-terminal probrain natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI) (Pedersen et al., 1999; Hansson et al., 2002; Spratt et al., 2005; Serres et al., 2006 and 2008; DeFrancesco et al., 2007; Bonagura and Schober, 2009; Serres et al., 2009; Terzo et al., 2009; Moonarmart et al., 2010; de Madron et al., 2011; Wolf et al., 2012; Nakamuraet al., 2014; Sargent et al., 2015).

Although several studies have evaluated the diagnostic value of known echocardiographic markers and cardiac biomarkers for detecting heart disease and heart failure, no study has evaluated those markers comprehensively in a single study population, to date. Because the diagnostic values of each marker tested vary according to the composition of study population and researchers, the aim of this study was to evaluate the diagnostic values of several echocardiographic markers and cardiac biomarkers for detecting heart disease and heart failure in a single study population (dogs with CMVI) consisting of small breeds of dogs, which would more closely reflect affected canine population in Asian countries.

Materials and Methods

***Study population*:** Fifty-one dogs with CMVI and body weights that matched 18 healthy control dogs were enrolled in this study. The diagnosis of CMVI and CHF stages was based on echocardiographic evidence of nodular thickening of the mitral valve, turbulent regurgitant flow into the LA, increased LA/Ao ratio, increased LVIDd/Ao ratio, increased transmitral E-peak velocity (E-peak) and valvular prolapse. The stage of heart failure was determined by International Small Animal Cardiac Health Council (ISACHC; The International Small Animal Cardiac Health Council, 1999). Dogs with other systemic diseases (e.g. diabetes, adrenal and thyroid diseases, hepatic diseases, and renal failure) were excluded from the study. Some dogs in ISACHC II and III groups were on medication with furosemide, pimobendan, enalapril and spirolonolactone before enrolling in this study. The healthy control dogs were selected based on no signs of heart diseases and other systemic diseases from echocardiography and routine laboratory tests. Based on ISACHC staging, the dogs with ISACHC I were regarded as dogs with heart disease (asymptomatic heart failure), while the dogs with ISACHC II and III were regarded as dogs with heart failure (symptomatic heart failure).

Measurement of echocardiographic markers: Echocardiographic examinations were conducted in accordance with recommended standards for dogs, using an ultrasound machine (X-300, Simens, Germany) with a 3-9 MHz sector probe. M-mode, Doppler, and 2-dimensional echocardiography were performed in left and right lateral recumbency. M-mode echocardiography was used to measure left ventricular dimension at systole (LVIDs) and diastole (LVIDd). Two-dimensional echocardiography was used to measure LA/Ao ratio and LVID/Ao ratio (Thomas, 1984). Pulsed-wave and continuous Doppler echocardiography were used to measure transmitral E-peak and septal (sE/Ea) and parietal Ea (pE/Ea) velocities from the left parasternal apical 4 chamber plane at the tips of the mitral valve when opened. End systolic volume index (ESVI) and end diastolic volume index (EDVI) were calculated by the following equation: LV volume (V) = $[(7 \times D^3) / (2.4 + D)]$ / body surface area (m^2) (Serres et al., 2008). Indexed LA diameter (iLA) and LVIDd (iLVID) were calculated by using the following formula: LA diameter (mm) / K, and LVIDd (mm) / K, respectively, K = $(0.795 \times \text{body weight [kg]})^{1/3}$.

Measurement of cardiac biomarkers: Blood samples w ere collected from either the jugular or cephalic veins i n blood tubes and were centrifuged within 30 minutes after collection, then the plasma was separated. Plasm a cTnI concentration was determined using a human A ccess AccuTnI assay (Beckman Coulter, Inc., Fullerton, CA) which was validated previously in dogs (Spratt et al., 2005). Plasma NT-proBNP concentrations were det ermined using an enzyme immunoassay for canine NT -proBNP (Cardiopet proBNP, IDEXX Laboratories) wh ich was validated previously in dogs (Serres et al., 200 9).

Statistical Analysis: Data are shown as mean±standard deviation. Statistical significance was defined as P<0.05. Normal distribution was confirmed by Kolmogorov-Smirnov test. One-way ANOVA test was performed to compare each parameter among study groups with Dunnett's test for post hoc analysis. Receiver-operating characteristic (ROC) analyses of each echocardiographic markers and cardiac biomarkers were used to assess predictive accuracy for detecting heart disease and heart failure in this study population. Statistical software used in statistical analysis was SPSS 15.0 for Windows (IBM, NY, USA).

Results

Characteristics of study population: The characteristics of the study population are listed in Table 1. Age of the CMVI groups was much older than that of the control group. Female was predominant in all study groups (Table 1). Body weight and BSA were slightly different among the study groups (Table 1). Malteses and Shih Tzus were the predominant dog breeds in this study group.

Statistical difference in echocardiographic markers and cardiac biomarkers in the study population: iLA, LA/Ao and LVIDd/Ao were significantly different between the control and CMVI groups (P<0.05) and between the ISACHC I and ISACHC II & III groups (P<0.05; Table 2). However, the LVIDd/Ao ratio was lower in the ISACHC I group than in the control group, while LVIDd was increased in the CMVI dogs (Table 2). iLVIDd was not different among the groups except in the ISACHC III groups (Table 2). EDVI was also different between the control and CMVI groups (P<0.05; Table 2), while ESVI was not significantly different between the control and CMVI groups, although the ISACHC III dogs had much higher ESVI than the control and other CMVI dogs (P<0.05; Table 2). The E-peak and sE/Ea and pE/Ea ratios were significantly different between the control and CMVI groups (P<0.05) and between the ISACHC I and ISACHC II & III groups (P<0.05; Table 2). The cTnI concentration was not significantly different between the control and CMVI groups and between the ISACHC I and ISACHC II & III groups (Table 2), while the NT-proBNP concentration was significantly different between the control and CMVI groups (P<0.05) and between the ISACHC I and ISACHC II & III groups (P<0.05; Table 2).

Table 1 Demographic distribution of the study population

	Control	ISACHC I	ISACHC II	ISACHC III
N	18	15	16	20
Age (yrs)	3.3±2.5	11.5±2.9	12.0±3.0	12.2±3.3
Gender	M (7), F(11)	M (6), F (9)	M (3), F (13)	M (8), F(12)
Body weight (kg)	3.1±1.4	4.1±1.8	3.7±1.0	4.0±1.3
Body surface area	0.21±0.06	0.26±0.08	0.24±0.44	0.25±0.06
Breed	YT (4), MA (7), ST (2), MP (2), PE (1), MS (2)	MA (7), ST (5), MS (1), MX (1), PO (1)	YT (5), MA (5), ST (4), PO (1), MP (1)	YT (4), MA (6), ST (5), PO (1), CH (1), MS (1), MP (2)

YT, Yorkshire terrier; MA, Maltese; ST, Shih Tzu; MP, Toy Poodle; PE, Pekingese; MS, Miniature Schnauzer; PO, Pomeranian; MX, Mixed; CH, Chihuahua; M, male; F, female; ISACHC, International Small Animal Cardiac Health Council

Table 2 Echocardiographic variables for predicting progression of heart failure from chronic mitral valvular insufficiency in the study population

	Control	ISACHC I	ISACHC II	ISACHC III
%FS	45.2±4.9	46.9±10.2	50.3±8.1*	51.6±11.3*,#
LVIDd (mm)	18.4±4.9	20.6±4.8	21.3±3.9	25.0±5.4*,#
LA/Ao	1.17±0.11	1.32±0.12*	1.59±0.10*,#	2.08±0.23*,#
LVIDd/Ao	1.70±0.29	1.58±0.29	1.87±0.32#	2.47±0.62*,#
iLA (mm)	10.4±1.6	14.2±4.0*	15.1±2.1*,#	17.7±2.4*,#
iLVIDd (mm)	16.2±3.1	16.7±0.4	17.6±2.2	20.2±4.7*,#
ESVI (mL/m²)	11.9±5.5	12.6±8.1	11.0±6.4	18.3±13.8
EDVI (mL/m²)	46.3±20.6	61.1±33.2*	65.0±22.7*	98.3±48.8*,#
E-peak (cm/sec)	65±9	79±12*	81±10*,#	125±27*,#
sE/Ea	6.7±1.3	7.2±1.2	10.4±1.7*,#	9.7±1.5*,#
pE/Ea	6.9±1.5	6.9±1.2	9.1±1.7*,#	10.8±1.1*,#
cTnI (ng/L)	0.01±0.01	0.02±0.01	0.02±0.02	0.03±0.02
NT-proBNP (pmol/L)	472±262	1329±494*	2096±820*,#	3247±1569*,#

%FS, fractional shortening; LVIDd, left ventricular dimension at diastole; LA/Ao, left atrium to aorta ratio; LVIDd/Ao, left ventricular diastolic dimension to aorta ratio; iLA, indexed left atrial diameter; iLVIDd, indexed left ventricular dimension at diastole; ESVI, end systolic volume index; EDVI, end diastolic volume index; E-peak, transmitral E-peak velocity; sE/Ea, ratio of early filling to early diastolic mitral annular velocity of septal wall; pE/Ea, ratio of early filling to early diastolic mitral annular velocity of parietal wall; cTnI, cardiac troponin I; NT-proBNP, N-terminal probrain natriuretic peptide; ISACHC, International Small Animal Cardiac Health Council. *, P<0.05 in control *vs* disease groups; #, P<0.05 in ISACHC I *vs* ISACHC II and III.

***Diagnostic value of echocardiographic markers and cardiac biomarkers in the study population*:** Receiver-operating characteristic (ROC) analyses of each echocardiographic markers and cardiac biomarkers were done to assess the predictive accuracy for detecting heart disease and heart failure in this study population (Figures 1 and 2). Based on the ROC analysis, the cut-off values for indicating heart disease

were %FS >47.4%, iLA >11.9 mm, LA:Ao >1.32, LVIDd >23.0 mm, LVIDd/Ao >1.91, ESVI >18.4 mL/m², EDVI >66.0 mL/m², iLVDd >19.4 mm, E-peak >80 cm/sec, sE/Ea >7.0, pE/Ea >6.9, cTnI >0.01 ng/mL and NT-proBNP >980 pmol/L, while the cut-off values for indicating heart failure were %FS >48.7%, iLA >12.7 mm, LA:Ao >1.58, LVIDd >23.1 mm, LVIDd/Ao >2.08, ESVI >23.0 mL/m², EDVI >80.3 mL/m², iLVIDd >19.4 mm, E-peak >90 cm/sec, sE/Ea >9.0, pE/Ea >8.9, cTnI >0.02 ng/mL and NT-proBNP >1200 pmol/L (Tables 3 and 4). The most sensitive markers for detecting heart disease in order were iLA, LA/Ao, NT-proBNP, E-peak, sE/Ea, cTNI, EDVI, %FS, pE/Ea, LVIDd, LVIDd/Ao, iLVIDd and ESVI, while the most specific markers were LVIDd, iLVIDd, E-peak, NT-ProBNP, sE/Ea, iLA, LA/Ao, pE/Ea, ESVI, LVIDd/Ao, %FS, EDVI, and cTnI (Table 3). Among the markers, iLA, LA/Ao, E-peak and NT-proBNP were the most reliable markers for detecting heart disease (P<0.00001; Table 3, Figure 1). The most sensitive markers for detecting heart failure in order were LA/Ao, iLA, E-peak, sE/Ea, NT-proBNP, %FS, pE/Ea, LVIDd/Ao, LVIDd, iLVIDd, cTnI, EDVI, and ESVI, while the most specific markers were LA/Ao, EDVI, ESVI, pE/Ea, sE/Ea, E-peak, cTnI, LVIDd, iLVIDd, NT-proBNP, iLA, LVIDd/Ao, and %FS (Table 3). Among the markers, LA/Ao, E-peak, sE/Ea and NT-proBNP were the most reliable markers for detecting heart failure (P<0.00001; Table 3, Figure 2).

Table 3 Area under receiver operating characteristic curve and optimal diagnostic cut-offs for detecting heart disease in dogs with chronic mitral valvular insufficiency

	Unit	Cut-off	AUC (96% CI)	Sensitivity	Specificity	P-value
%FS	%	>47.4	0.692 (0.569-0.797)	54.9	88.9	0.0029
iLA	mm	>11.9	0.953 (0.873-0.989)	90.2	94.4	0.00001
LVIDd	mm	>23.0	0.741 (0.622-0.839)	47.1	100	0.0001
LA/Ao		>1.32	0.944 (0.861-0.985)	88.2	94.4	0.00001
LVIDd/Ao		>1.91	0.557 (0.432-0.676)	37.2	88.9	0.4277
ESVI	mL/m²	>18.4	0.517 (0.394-0.639)	27.5	94.4	0.8156
EDVI	mL/m²	>66.0	0.681 (0.558-0.788)	58.3	72.7	0.0049
iLVIDd	mm	>19.4	0.642 (0.517-0.754)	35.3	100	0.0367
E-peak	cm/sec	>80	0.931 (0.844-0.978)	74.5	100	0.00001
sE/Ea		>7.0	0.878 (0.777-0.944)	68.7	100	0.00001
pE/Ea		>6.9	0.794 (0.679-0.882)	52.9	94.4	0.00001
cTnI	ng/mL	>0.01	0.662 (0.539-0.772)	66.7	57.5	0.0085
NT-proBNP	pmol/L	>980	0.980 (0.913-0.999)	88.2	100	0.00001

%FS, fractional shortening; LVIDd, left ventricular dimension at diastole; LA/Ao, left atrium to aorta ratio; LVIDd/Ao, left ventricular diastolic dimension to aorta ratio; iLA, indexed left atrial diameter; iLVIDd, indexed left ventricular dimension at diastole; ESVI, end systolic volume index; EDVI, end diastolic volume index; E-peak, transmitral E-peak velocity; sE/Ea, ratio of early filling to early diastolic mitral annular velocity of septal wall; pE/Ea, ratio of early filling to early diastolic mitral annular velocity of parietal wall; cTnI, cardiac troponin I; NT-proBNP, N-terminal probrain natriuretic peptide; ISACHC, International Small Animal Cardiac Health Council. *, P<0.05 in control *vs* disease groups; #, P<0.05 in ISACHC I *vs* ISACHC II and III.

Table 4 Area under receiver operating characteristic curve and optimal diagnostic cut-offs for detecting heart failure in dogs with chronic mitral valvular insufficiency

	Unit	Cut-off	AUC (96% CI)	Sensitivity	Specificity	P-value
%FS	%	>48.7	0.689 (0.566-0.795)	75	66.7	0.0047
iLA	mm	>12.7	0.891 (0.793-0.953)	97.2	75.8	0.00001
LVIDd	mm	>23.1	0.723 (0.602-0.824)	50	87.9	0.0003
LA/Ao		>1.58	0.994 (0.948-1.000)	100	100	0.00001
LVIDd/Ao		>2.08	0.745 (0.625-0.842)	69.4	75.8	0.00001
ESVI	mL/m²	>23.0	0.535 (0.411-0.656)	19.4	97	0.6175
EDVI	mL/m²	>80.3	0.653 (0.528-0.763)	37.3	100	0.0217
iLVIDd	mm	>19.4	0.678 (0.555-0.786)	44.4	84.9	0.0057
E-peak	cm/sec	>90	0.987 (0.924-1.000)	97.2	91	0.00001
septal E/e'		>9.0	0.978 (0.910-0.998)	91.7	94	0.00001
Parietal E/e'		>8.9	0.916 (0.824-0.969)	75	97	0.00001
cTnI	ng/mL	>0.02	0.694 (0.571-0.799)	41.2	88.9	0.0011
NT-proBNP	pmol/L	>1200	0.926 (0.837-0.975)	88.9	78.9	0.00001

%FS, fractional shortening; LVIDd, left ventricular dimension at diastole; LA/Ao, left atrium to aorta ratio; LVIDd/Ao, left ventricular diastolic dimension to aorta ratio; iLA, indexed left atrial diameter; iLVIDd, indexed left ventricular dimension at diastole; ESVI, end systolic volume index; EDVI, end diastolic volume index; E-peak, transmitral E-peak velocity; sE/Ea, ratio of early filling to early diastolic mitral annular velocity of septal wall; pE/Ea, ratio of early filling to early diastolic mitral annular velocity of parietal wall; cTnI, cardiac troponin I; NT-proBNP, N-terminal probrain natriuretic peptide; ISACHC, International Small Animal Cardiac Health Council. *, P<0.05 in control *vs* disease groups; #, P<0.05 in ISACHC I *vs* ISACHC II and III.

Discussion

Early detection of heart disease and heart failure is a key success for managing heart disease in dogs. However, early detection is often challenging in dogs with asymptomatic heart diseases. Therefore, current researches are directed to detect heart disease and heart failure at an earlier stage as possible. In

addition, the differentiation of symptomatic heart disease (i.e. heart failure stage) from asymptomatic heart disease is also important for minimizing complications from long-term medical management in dogs with heart failure. Although several echocardiographic markers and cardiac biomarkers have been found to be useful for earlier detection of heart disease and for precise prediction of progression in dogs, the sensitivity and specificity of each marker vary among researches (Pedersen et al., 1999; Hansson et al., 2002; Spratt et al., 2005; Serres et al., 2006 and 2008; DeFrancesco et al., 2007; Bonagura and Schober, 2009; Serres et al., 2009; Terzo et al., 2009; Moonarmart et al., 2010; de Madron et al., 2011; Wolf et al., 2012; Nakamura et al., 2014; Sargent et al., 2015). Therefore, a more comprehensive study using a more appropriate study population to reflect disease population is necessary to develop standard guidelines for successful management of detecting heart disease and heart failure in dogs.

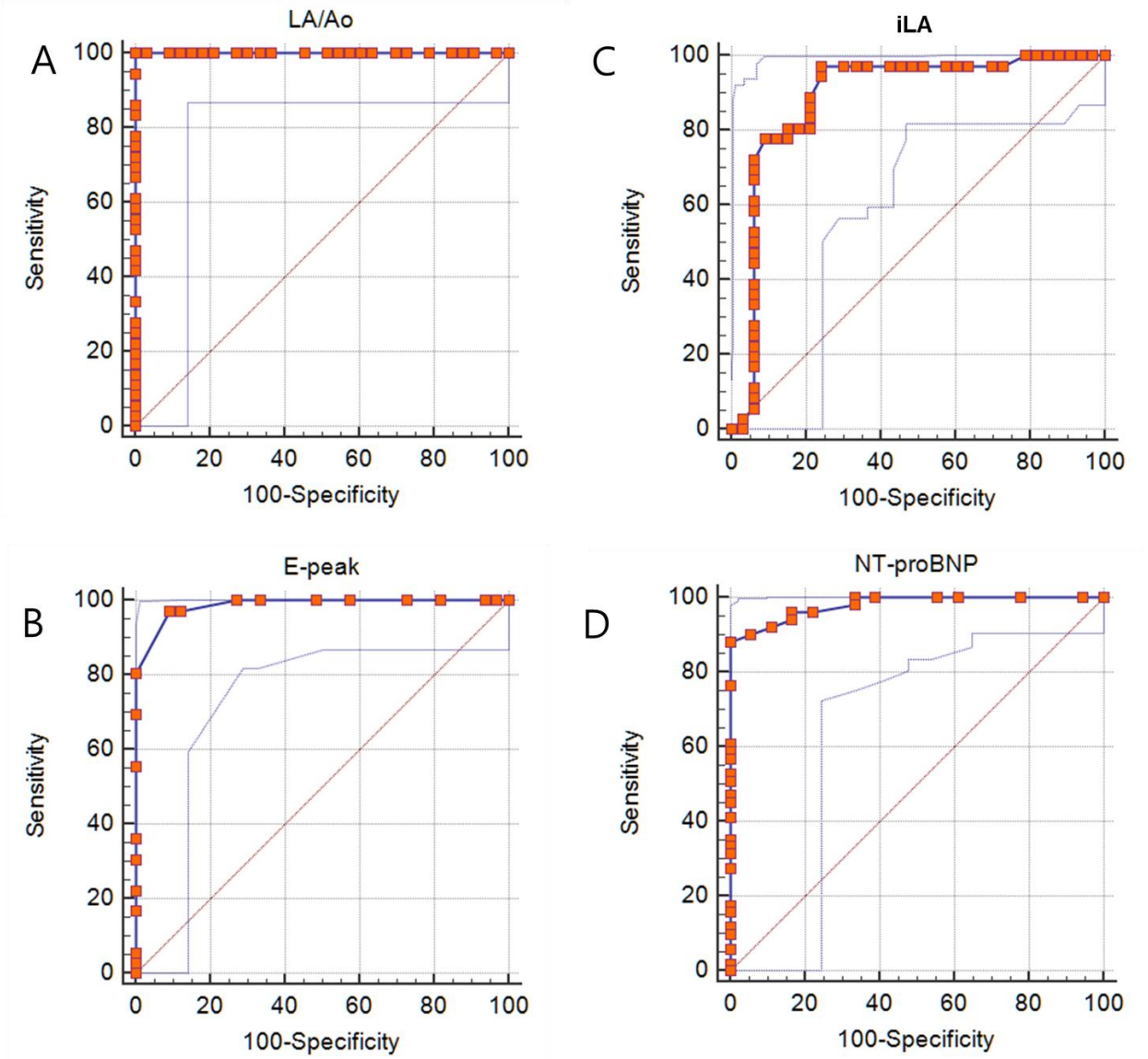


Figure 1 Receiver-operating characteristic (ROC) analyses of left atrium to aorta ratio (A: LA/Ao), transmitral E-peak velocity (B: E-peak), indexed left atrial diameter (C: iLA) and N-terminal probrain natriuretic peptide (D: NT-proBNP) for assessing predictive accuracy for detecting heart disease in the study population

Echocardiography is a non-invasive and popular diagnostic method for detecting heart diseases and evaluating the progression of heart failure from any heart disease in dogs. Diagnostic values for several echocardiographic markers have been evaluated in dogs with CMVI (Pedersen et al., 1999; Hansson et al., 2002; Serres et al., 2006 and 2008; Bonagura and Schober, 2009; Terzo et al., 2009; de Madron et al., 2011; Nakamura et al., 2014; Sargent et al., 2015). Common echocardiographic markers for detecting heart disease and evaluating the severity of heart failure are LA/Ao, LVIDd/Ao, transmitral E-peak, EDVI, and maximal area of the regurgitant jet signals to the left atrium area (ARJ/LAA) ratio (Boon, 1998). Furthermore, recent studies have found that co-existence of pulmonary hypertension (i.e. evidenced by the presence of tricuspid and/or pulmonic regurgitation jets) might exacerbate clinical signs in dogs with CMVI (Chiavegato et al., 2009; Stepien, 2009).

In this study, those known echocardiographic markers for dogs correlated well with the presence of heart disease and the severity of heart failure in dogs with CMVI. However, the diagnostic sensitivity and specificity were not strong enough in certain

echocardiographic markers. For instance, LVIDd, iLVIDd and LVDd/Ao reflecting LV dilation had higher specificity for detecting heart disease and heart failure in this study population. However, these echocardiographic markers had lower sensitivity for detecting heart disease and heart failure in this study population, leading to misdiagnosis in this study. A recent study has suggested that body weight indexed parameters (i.e. iLVIDd, iLA diameter) could provide more accurate measurement of echocardiographic dimensions in dogs because dogs had marked variation among breeds. However, in this study, the diagnostic value of iLVIDd was slightly different from that of LVIDd, suggesting that several factors other than chest conformation might affect LV internal dimensions in dogs, although echocardiographic measurement of LV dimensions might be more consistently measured by experienced echocardiographers. Interestingly, the iLA diameter had higher sensitivity and specificity for detecting heart disease, although it had lower specificity for detecting heart failure in this study population. In dogs with left-sided congestive heart failure (e.g. CMVI), the volume and size of LA closely correlated with the severity of heart disease and heart failure. However, in practice, accurate and consistent measurement of LA diameter using two-dimensional assessment of LA with linear methods is often difficult to achieve because the actual structure of LA is three-dimensional. Therefore, recent studies have suggested the volume-based methods of chamber quantification using three-dimensional echocardiography (3DE). However, because 3DE is costly and is not routinely used in veterinary fields, LA/Ao and iLA might be good alternatives for assessing LA enlargement. In this study, LA/Ao and iLA had higher sensitivity and specificity for detecting heart disease and differentiating dogs with heart disease from heart failure.

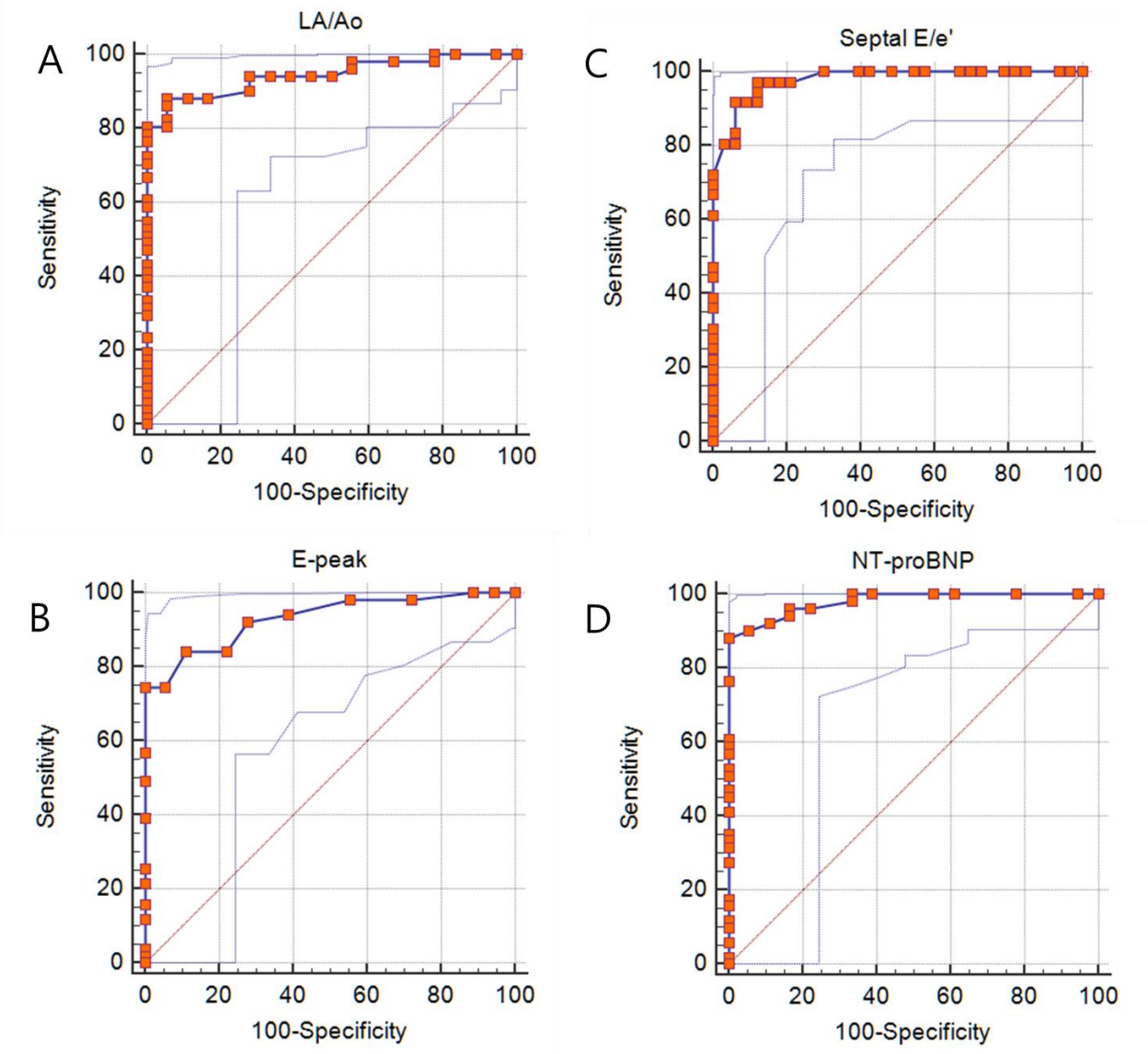


Figure 2 Receiver-operating characteristic (ROC) analyses of left atrium to aorta ratio (A: LA/Ao), transmitral E-peak velocity (B: E-peak), ratio of early filling to early diastolic mitral annular velocity of septal wall (C: Septal E/e') and N-terminal probrain natriuretic peptide (D: NT-proBNP) for assessing predictive accuracy for detecting heart disease in the study population

LV systolic myocardial dysfunction is an indicative sign of heart failure and is generally assessed by ejection fraction (%EF) and fractional shortening (%FS) in echocardiography. %FS is a %change in the LV dimension from end diastole to end systole (Sargent et al., 2015). Although %FS is reduced in human patients with myocardial dysfunction (Enriquez-Sarano et al., 1994), it is increased in dogs with CMVI due to hyperdynamic ventricular contraction from elevated preload and reduced afterload (Kittleson et al., 1984). In this study, %FS was increased in the CMVI dogs and the dogs with more advanced stage of heart failure. However, the diagnostic value of this marker was not high enough to detect heart disease and predict heart failure in this study population. Recent canine studies have found that systolic myocardial dysfunction was more accurately identified by end-systolic left ventricular dimensions, such as ESVI and EDVI, which were indexed to body surface area (BSA) (Kittleson et al., 1984; Serreset al., 2008; Bonagura et al., 2009). Increased ESVI and EDVI were consistently found in CMVI dogs with advanced stage of heart failure (Serres et al., 2008). In this study, the diagnostic values of EDVI and ESVI were not high enough to detect heart disease and predict heart failure. Although EDVI was increased in the dogs with more advanced stage of heart failure, ESVI could not discriminate the dogs with CMVI from the healthy dogs. Because the Teichholz method based on M-mode echocardiographic measurement of LV dimension often overestimates ESVI and EDVI, the poorer diagnostic values of EDVI and ESVI in this study than in previous studies (Kittleson et al., 1984; Serreset al., 2008) might be due to the echocardiographic measurement for LV dimension (i.e. only Teichholz method used in this study).

The severity of LV volume and pressure overload by MR can be assessed by Doppler patterns of transmitral inflow. The transmitral flow profile consisting of E and A is affected by the pressure gradient between LA and LV. Elevated E represents increased LA pressure and worsening of heart failure (Borgarelli et al., 2008). In this study, the E-peak had higher sensitivity and specificity for detecting heart disease and differentiating the dogs with heart disease from those with heart failure, as previously reported (Buchanan, 1999; de Madron et al., 2011; Nakamura et al., 2014). According to recent guidelines for dogs with CMVI, >80 cm/sec E-peak is indicative of deteriorating signs of heart disease in dogs, as similarly noticed in this study.

The elevation of LA pressure (LAP) is the most common pathological signs in dogs with CMVI. Direct measurement of LAP with cardiac catheterization is the most accurate method. However, this method is too invasive and requires anesthesia, thus echocardiographic estimation of LAP such as including E/Ea ratio is rapidly replacing the catheter based measurement. One recent study has found that the E/Ea ratio correlated well with the mean LAP in dogs (Oyama et al., 2004). E/Ea might be more accurate in reflecting LA volume and pressure overload in dogs with heart diseases because the Ea-peak on tissue Doppler echocardiography is minimally affected by loading conditions, unlike the transmitral E-peak. In this study, the diagnostic values of sE/Ea and pE/Ea were high enough to detect heart disease and predict heart failure. These two parameters could also discriminate the symptomatic heart failure dogs from the asymptomatic dogs. One recent study has evaluated the relationship between E/Ea and mean LAP in dogs with experimentally induced MR (Oyama et al., 2004) and found that E/Ea <6.0 and >9.1 indicated the mean LAP <20 mmHg and >20 mmHg, respectively, suggesting that E/Ea >9.1 might be indicative of advanced stage heart failure. In this study, the cut-off values of sE/Ea and pE/Ea for heart disease and heart failure were ~7.0 and ~9.0, respectively. This result is well concordant with a previous study and suggested that E/Ea might be a good marker for LA enlargement in dogs. However, the measurement of Ea is angle-dependent, the accurate alignment of the Doppler beam to mitral annulus must be maintained for consistent estimation of Ea.

Cardiac biomarkers have been used for differentiating cardiac diseases from respiratory diseases and for predicting the progression of heart failure in dogs and cats (Spratt et al., 2005; DeFrancesco et al., 2007; Serres et al., 2009; Moonarmart et al., 2010; Wolf et al., 2012). cTnI and NT-proBNP are the most commonly tested cardiac biomarkers in dogs and humans. cTnI levels are closely related to levels of myocardial necrosis and ischemia (Spratt et al., 2005), while levels of NT-proBNP are closely related to hemodynamic stress on cardiac chambers from volume expansion/pressure overload in dogs (Serres et al., 2009; Wolf et al., 2012). In this study, the diagnostic value of cTnI was not high enough to detect heart disease and heart failure, although >0.02 ng/L cTnI was the indicative value of heart disease and heart failure in this study population. Unlike cTnI, the diagnostic value of NT-proBNP was high enough for earlier detection of heart disease and for more accurate differentiation of symptomatic heart failure dogs from asymptomatic heart failure dogs. The cut-off values for detecting heart disease and heart failure in this study were >980 pmol/L and >1200 pmol/L, respectively. According to recent guidelines from the manufacturer, >900 pmol/L of NT-proBNP was indicative of heart disease and 900-1800 pmol/L was indicative of heart failure, which is well concordant with our study.

Based on the ROC analysis of echocardiographic parameters and cardiac biomarkers in this study, the indications for healthy dogs or dogs with no signs of cardiac enlargement were iLA <11.9 mm, LVIDd <23.0 mm, LA/Ao <1.32, LVIDd/Ao <1.91, ESVI <18.4 mL/m^2, EDVI <66.0 mL/m^2, iLVIDd >19.4 mm, E-peak <80 cm/sec, septal E/Ea <7.0, pE/Ea <6.9, cTnI <0.01 ng/mL and NT-proBNP <980 pmol/L. The %FS >48.7%, iLA >12.7 mm, LA/Ao >1.58, LVDd >23.1 mm, LVDd/Ao >2.08, ESVI >23.0 mL/m^2, EDVI >80.3 mL/m^2, iLVDd >19.4 mm, E-peak >90 cm/sec, sE/Ea >9.0, pE/Ea >8.9, cTnI >0.02 ng/mL and NT-proBNP >1200 pmol/L were indicative of advanced stage of heart failure in this study, which agrees well with previous reports (de Madron et al., 2011; Nakamura et al., 2014; Suh et al., 2016).

In this study, there were several limitations. Firstly, the age of the control group did not match that of the CMVI group, influencing the echocardiographic

variables. Because the ventricular wall and vascular wall generally get stiffer with age, the loading conditions might be different between healthy young dogs and aged CMVI dogs. Further study using age-matched control dogs is necessary to verify these study results. Secondly, some dogs in the ISACHC II and III groups were under medication (e.g. diurectic, vasodialtors and inotropics), which could significantly affect the loading conditions. Therefore, underestimation of any echocardiographic variable could possibly occur if the variable was load-dependent, although this effect might not significantly affect the overall study findings. Lastly, there were technical difficulties of correct measurement of septal and parietal Ea-peak on the tissue Doppler echocardiography if the heart was too deviated from the original location. Because incorrect beaming and unclear visualization could lead to incorrect estimation of sE/Ea and pE/Ea, there was a chance for incorrect measurement in these dogs, although the consistency and accuracy were maintained by one experienced sonographer.

In conclusion, this study evaluated the diagnostic values of known echocardiographic parameters and cardiac biomarkers for detecting heart disease and heart failure in a single study population (dogs with CMVI) consisting of small breeds of dogs, which could more closely reflect affected canine population in Asian countries. Based on the ROC analyses of each echocardiographic parameters and cardiac biomarkers for assessing the predictive accuracy for detecting heart disease and heart failure in this study population, iLA, LA/Ao, E-peak, E/Ea and NT-proBNP were the most reliable and consistent parameters for detecting heart disease and differentiating symptomatic heart failure dogs from asymptomatic dogs with CMVI. This is the first canine study to comprehensively evaluate known echocardiographic markers and cardiac biomarkers in a single study population.

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บทคัดย่อ

ค่าการวินิจฉัยของดัชนี echocardiographic และ cardiac biomarkers ในสุนัขที่มีภาวะ chronic mitral valve insufficiency

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สุนัขที่เป็นโรคหัวใจอาจไม่แสดงอาการภาวะหัวใจล้มเหลว ดังนั้นการกำหนดรูปแบบ ภาวะหัวใจล้มเหลวในสุนัขที่มีโรคหัวใจจึงมีความสำคัญ การศึกษาครั้งนี้ได้ประเมินค่าการวินิจฉัยของปัจจัย echocardiographic parameters และ cardiac biomarkers เพื่อคัดแยกสุนัขที่มีโรคหัวใจซึ่งแสดงอาการหรือไม่แสดงอาการภาวะหัวใจล้มเหลว โดยศึกษาในสุนัขจำนวน 51 ตัวที่มี chronic mitral valvular insufficiency (CMVI) และแสดงภาวะหัวใจล้มเหลวที่แตกต่างกัน และ สุนัขกลุ่มควบคุมที่มีสุขภาพดีจำนวน 18 ตัว โดยศึกษาพารามิเตอร์ echocardiographic และ biomarkers ผลการศึกษาพบว่ามีความแตกต่างอย่างมีนัยสำคัญในการจัดทำดัชนี left atrial diameter (iLA) left atrial to aorta ratio (LA/Ao), left ventricular diastolic dimension to aorta ratio (LVIDd/Ao), transmitral E-peak (E-peak), septal E/Ea ratio (sE/Ea), parietal E/Ea ratio (pE/Ea) และ N-terminal probrain natriuretic peptide (NT-proBNP) ระหว่างสุนัขกลุ่มควบคุมและสุนัขที่มี CMVI (P <0.05) และ ระหว่างสุนัขแสดงอาการและไม่แสดงอาการ (P <0.05) ค่าดัชนีขั้นต่ำสำหรับบ่งชี้โรคหัวใจในสุนัขในการศึกษาครั้งนี้คือค่า ILA> 11.9 มม, LA:Ao > 1.32 LVIDd/Ao > 1.91 E-peak > 80 ซม. / วินาที sE / Ea> 7.0, pE / Ea> 6.9, และ NT-proBNP> 980 pmol /L ในขณะที่ค่าดัชนีขั้นต่ำสำหรับการบ่งชี้ภาวะหัวใจล้มเหลว คือค่า ILA> 12.7 มิลลิเมตร, LA:Ao > 1.58 LVIDd/Ao > 2.08 E-peak > 90 ซม. / วินาที sE / Ea> 9.0, PE / Ea> 8.9, และ NT-proBNP> 1200 pmol / L การศึกษานี้แสดงให้เห็นว่า iLA, LA/Ao, E-peak, E/Ea และ NT-proBNP เป็นดัชนีที่น่าเชื่อถือและมีความสม่ำเสมอในการตรวจหาโรคหัวใจและความแตกต่างของสุนัขที่มีอาการและไม่มีอาการภาวะหัวใจล้มเหลวจาก CMVI

คำสำคัญ: echocardiography, cardiac biomarker ภาวะหัวใจล้มเหลว สุนัข mitral valve insufficiency

สาขาอายุรศาสตร์สัตว์เล็ก วิทยาลัยสัตวแพทยศาสตร์ มหาวิทยาลัยแห่งชาติคังวอน, ชุนชอน, สาธารณรัฐเกาหลี
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