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評估犬隻呼吸道與慢性心臟疾病相關性之研究

Evaluation of the Relationship between Canine Respiratory Disorders and Chronic Heart Disease

戴子綺

Tzu-Chi Tai

指導教授：黃慧璧博士

Advisor: Hui-Pi Huang, DVM, Ph.D.

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本論文係戴子綺君（R98643006）在國立臺灣大學臨床動物醫學研究所完成之碩士學位論文，於民國一百零一年七月十八日承下列考試委員審查通過及口試及格，特此證明

口試委員：黃財旺（簽名）

（指導教授）

系主任、所長（簽名）

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Abstract

The complex interactions among respiratory system, right and left heart may lead to the high comorbidity between the cardiorespiratory diseases. The hemodynamic alteration and vascular bed remodeling of the pulmonary circulation, systemic inflammation and hypoxia are the possible pathogenesis of cardiac functional and structural changes in respiratory system disorders. Ventricular interdependence mediated through interventricular septum, pericardium sac and transmitted myofibers may play an important role in the relationship of right and left heart failure. The ratio of tracheobronchial diameters to thoracic inlet distance and the angle of tracheal bifurcation on thoracic radiographs were estimated to investigate the relationship between chronic degenerative mitral valvular disease (CDMD) and tracheobronchial collapse in 54 clinically healthy small breed dogs and 79 dogs with CDMD at different conditions of modified New York heart association functional classification. The result indicated that narrowing of trachea and bronchus in dogs with CDMD developed where the anatomical regions directly contacted with the heart and the degree of tracheobronchial compression was associated with severity of CDMD. However, the study failed to identify that trachea collapse is one of the risk factors for development CDMD and left heart failure. In the second study, the echocardiographic right indices were measured in 40 clinically healthy dogs and 169 dogs with different causes of elevated pulmonary artery pressure. The result presented that right heart indices were affected differently by chronic respiratory disorders, heartworm disease and moderate to severe CDMD; chronic respiratory disorders and heartworm disease had significant effect on the deformation of the pulmonary vascular and right ventricle. The different ventricular interdependence among the three causes of elevated pulmonary artery pressure might be attributed to the interaction between the dilated right ventricle and the different conditions of left ventricle.

中文摘要

呼吸系統與左右心之間複雜的交互作用，可能導致心肺疾病有較高合併發生的機率。在呼吸系統疾病下造成心臟功能與結構改變的致病機轉可能來自於肺循環血流動力學的改變與血管床重塑，另外慢性炎症反應和缺氧也可能是誘發的原因之一。左右心間高度的依存關係來自於共同擁有的心室間隔、心包囊與結構上交錯的肌纖維，而這樣密切的交互作用在右心與左心衰竭的關係上可能扮演重要的角色。本論文包含兩個部分，第一項研究包含了五十四隻無心肺症狀的健康犬隻與一百三十三隻按照紐約心臟協會分級系統修正版 (modified New York heart association functional classification) 分組的退化性二尖瓣疾病犬，透過統計胸腔放射線數位影像上從氣管到支氣管共六個部位的氣管徑與入胸處寬度比例與左右主要之氣管交叉處的夾角在不同心衰竭分級犬隻上的差異去了解氣管與支氣管塌陷和退化性二尖瓣疾病的關係。結果顯示氣管塌陷與退化性二尖瓣疾病的發生並無直接相關性，也無法證明氣管塌陷是心衰竭的危險因子之一，而氣管與支氣管僅在心臟解剖學相關位置受到壓迫，且壓迫程度與心衰竭程度相關。第二項研究中使用心臟超音波測量四十隻健康無心肺症狀犬隻與其他分別因呼吸道疾病、犬心絲蟲病與退化性二尖瓣心臟病而提升肺動脈壓力的一百六十九隻病犬，以超音波測得右心參數來評估不同病因導致的肺高壓對於右心功能之影響。結果顯示不同病因導致的肺高壓可能會造成不同程度的右心塑形，其中以心絲蟲與呼吸道疾病導致之肺動脈高壓對肺動脈與右心結構上的影響程度較為顯著。而在這三種造成肺動脈高壓的疾病間，左右心交互作用的差異可能來自於心絲蟲，呼吸道疾病以及退化性二尖瓣疾病間左右心狀態與壓力上的不同。

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Chapter 1
General Introduction

Abbreviations:

LV	left ventricle
PAH	pulmonary artery hypertension
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PH	Pulmonary hypertension
PVR	pulmonary vascular resistance
RV	right ventricle
TPG	transpulmonary pressure gradient

The relationship between respiratory and cardiovascular system

The closely interactions between the respiratory and cardiovascular systems have been increasingly appreciated.[1-4] The right atrium and ventricle received the deoxygenated blood from systemic circulation, and then pumps the flow to the pulmonary circulation. The flow of blood passes through the pulmonary artery to the pulmonary capillaries, where carbon dioxide is exchanged for oxygen derived from the respiratory tract, then back through the pulmonary vein to the left atrium, left ventricle and systemic circulation.[5,6] Although the same stroke volume is pumped by both ventricles, the right and left part of the heart are designed differently to cope with the pulmonary and systemic circulation.[7] In normal conditions, the pulmonary vascular bed is a low resistance and high capacitance system that is capable of accommodating large amounts of blood flow at low level of pulmonary arterial and capillary pressure and provides the pulmonary alveolus and capillaries with highly efficient gas-exchange ability.[8] The right ventricle (RV) is thin walled, compliant, and low-pressure chambers that can adapt rapid changes in volume load of systemic circulation and has a lower stoke work compared with left ventricle (LV) because of the low hydraulic impedance of the pulmonary vascular bed.[6,9] The muscular LV shares the pericardial sac, the interventricular septum, and the myofibers with the RV.[10,11] Ventricular interdependence defined as the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium is a consequence of the close anatomic arrangement between the ventricle.[12,13]

In macroscopically anatomic studies, the notion that both RV and LV exist as a continuous muscle band, extending from the pulmonary artery to the aorta and coiled into transverse basal and oblique apical loops, has been proposed.[10,14] In the recent diffusion tensor MRI research of the canine heart, the observation that the superficially circumferential muscle layers wrap around both the RV and LV also

support the close relationship of RV and LV architecture.[15] Furthermore, left ventricular contraction contributes partial stroke work to the generation of right ventricular stroke work via the septum, and a dilated RV resulted from increased pulmonary vascular resistance debilitates the systolic support of the RV generated by the LV were demonstrated in a canine experimental mode.[16]

The complex interactions among the respiratory system, the right and left heart lead to the high comorbidity between the respiratory disorders and cardiovascular diseases.

The cardiovascular sequelae of respiratory system disorders have been recognized for decades in human medicine.[17-19] The possible pathogenesis of cardiac manifestations in respiratory system disorders include systemic inflammation, oxidative stress, hypoxia, activation of the sympathetic nervous system, vascular dysfunction and connective tissue degradation.[17] The spectrum of cardiovascular diseases include right ventricular dysfunction associated with pulmonary hypertension, coronary artery disease, and arrhythmia.[20] In dogs, the most commonly described cardiovascular sequelae of respiratory system disorders are pulmonary hypertension and right heart dysfunction.[1,3,21,22]

Pulmonary hypertension

In veterinary medicine, Pulmonary hypertension (PH) has been described as echocardiographically-estimated pulmonary artery pressure (PAP) great than 25 mmHg.[1-3,23,24] The normal mean PAP at rest is about 14 mmHg.[25-27] Pulmonary hypertension develops when there are an increased pulmonary vascular resistance (PVR), increased pulmonary blood flow, or impedance of pulmonary venous drainage.[27,28] The increased pulmonary blood flow commonly occurs in association with congenital cardiac anomalies and the impedance of pulmonary venous drainage

usually results from impaired left heart function or structure.[3,27,29] The elevation of PVR may occur in the primary PH associated with specific gene mutations found in human medicine, thromboembolic diseases, parasites infestation, advanced respiratory tract disorders, uncompensated and reactively conditions of volume-overloaded pulmonary circulation.[26-31] The increase in PVR is related to an imbalance among the factors, such as thromboxane A_2, endothelin-2, serotonin, nitric oxide, and prostacyclin that control of pulmonary vascular tone, platelet activation, vascular remodeling and cell proliferation.[1,32,33] Hypoxia, inflammation, mechanical stress and abnormal pulmonary vascular pressure gradient are other associated environmental factors.[28,32] According to the hemodynamic definitions associated with pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and cardiac output, the PH can be classified as pre-capillary and post-capillary PH and according to the similarities of pathophysiologic mechanism, clinical presentation, and therapeutic characters in different diseases with PH, the clinical conditions can further categorized in five groups in human medicine. [34,35] This scheme of clinical classification has been adapted and modified in veterinary community (Table 1). [26,30]

Pre-capillary pulmonary hypertension

Pre-capillary PH is characterized by the elevated PAP resulted from increased pulmonary artery blood flow and PVR with nearly normal PCWP.[27,28,30] Primary or idiopathic pulmonary artery hypertension (PAH) has been described rarely in dogs.[36] An important cause of secondary pre-capillary PH in dogs is the *Dirofilaria immitis* infestation in endemic areas.[23,31,37] The thromboembolism, irreversible vascular structure damage and proliferation result in the increased PVR and elevated PAP in dogs with heartworm disease .[37] The hypoxic pulmonary vasoconstriction, hypoxic remodeling of pulmonary vascular bed, academia, hypercarbia, altered blood viscosity,

inflammation, and the distortion of pulmonary vessels by parenchymal changes in chronic respiratory diseases are other factors contribute to the increased PVR and the pre-capillary PH.[1,2,33,38,39] Other recognized causes in dogs include the congenital cardiac anomalies, pulmonary thromboembolism, and hypobaric hypoxia due to the exposure to high altitude.[1,3,40-42]

Post-capillary pulmonary hypertension

Post-capillary PH is characterized by the elevated PAP resulted from increased PCWP. The transpulmonary pressure gradient (TPG) calculated from mean PAP minus PCWP and the PVR are usually within the normal range in Left heart diseases with passively elevated PAP.[27,28,30] Chronic left heart disease, such as valvular and myocardial dysfunction leads to increased left atrial pressure and PCWP.[29,43] The left atrial pressure and PCWP depends on the left atrial size and compliance. [44] Under normal conditions, the PCWP is less than 10 mmHg. When the PCWP exceeds 25mmHg, the pulmonary edema and the congestive signs are developed in healthy individuals.[27,45] However, in cases with slowly progressing left heart diseases, the increased size and compliance of left atrium reserve the overloaded volume within the atrial cavity and the pulmonary vascular as well as alveolar remodeling reduce the permeability of the alveolar-capillary membrane; as a consequence, these changes in patients with long-standing left heart failure probably prevent the formation of pulmonary edema but may increase the PVR.[29,44,46,47] A reactive increase in the PVR associated with the pulmonary artery vasoconstriction due to acute hypoxia or the persistent structure changes in pulmonary vascular bed results in an increased TPG and reactive PH in left heart diseases.[30,46]

The right heart failure

The right ventricular dysfunction may be caused by pressure or volume overload, ischemia, intrinsic myocardial disease, or pericardial constraint. [6,48] The thin-walled and resilient RV tolerates volume overload better than pressure overload. Thus PH is an important cause of RV failure .[11] Increased afterload is the primary cause RV adaption in PH. Initially, the concentric remodeling of RV enhances the systolic contraction and the hypertrophic RV copes well with the increased afterload. [49] As the pressure overload persists and the contractile weakening progresses, the RV dilates to increase the compensatory preload and maintain stroke volume.[6,9] Consequences of RV dilation are an increased in cardiac wall tension, altered ventricular interdependence, and increased myocardial oxygen demand; the progressively dilated RV further impairs the contractility and leads to underfilling of the LV.[6,49,50] The hemodynamic changes and the progression in the conditions of PH are related to the complex pathophysiological interactions between the progression of the obstructive changes in the pulmonary microcirculation and the response of the overload RV.[51]

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Table 1. Modified clinical classification of pulmonary hypertension for dogs and cats

Classification of pulmonary hypertension
1. Pulmonary arterial hypertension
a. Heartworm disease
b. Congenital systemic-to-pulmonary shunts
i. Atrial septal defect (ASD)
ii. Ventricular septal defect (VSD)
iii. Patent ductus arteriosus (PDA)
2. Pulmonary hypertension with left heart disease
a. Mitral valve disease
b. Myocardial disease
c. Any left-sided heart disease
3. Pulmonary hypertension with pulmonary disease/hypoxia
a. Chronic obstructive pulmonary disease
b. Interstitial pulmonary fibrosis
c. Neoplasia
d. High-altitude disease
e. Reactive pulmonary artery vasoconstriction (pulmonary edema)
4. Pulmonary hypertension due to thrombotic and/or embolic disease
a. Thromboembolism
i. Immune-mediated hemolytic anemia
ii. Neoplasia
iii. Cardiac disease
iv. Protein-losing disease (nephropathy or enteropathy)
v. Hyperadrenocorticism
vi. Disseminated intravascular coagulation
vii. Sepsis
viii. Trauma
ix. Recent surgery
b. Heartworm disease
5. Miscellaneous
a. Compressive mass lesions (neoplasia, granuloma)

Chapter 2

Luminal Diameters of Trachea and Bronchi in Small Breed Dogs with and without Chronic Degenerative Mitral Valvular Disease

Abbreviations:

Ao	aortic root diameter
CDMD	degenerative mitral valvular disease
E/A	early diastolic velocity/late diastolic velocity ratio
EF	ejection fraction
FS	fractional shortening
IVS	thickness of interventricular septum
LA	left atrial diameter
LMB	left cranial main stem bronchus
LVED	left ventricular dimension
LVFWd	thickness of left ventricular free wall at end-diastole
MR	mitral valve regurgitation
NYHA	modified New York heart association functional classification
RMB	right cranial main stem bronchus
TB angle	angle of tracheal bifurcation
TBC	tracheobronchial collapse
TC	tracheal collapse
TD	tracheobronchial diameter
TI	thoracic inlet distance
TR	tricuspid regurgitation
VHS	vertebral heart scale

Luminal diameters of trachea and bronchi in small breed dogs with and without chronic degenerative mitral valvular disease

Tzu-Chi Tai, Hui-Pi Huang
Department of Veterinary Medicine, National Taiwan University, Taipei, Taiwan.

Abstract

Background: Chronic degenerative mitral valvular disease (CDMD) and tracheobronchial collapse (TBC) are common combination in small breed dogs.
Hypothesis: Trachea collapse (TC) is not one of the risk factors for development CDMD.
Animals: 54 clinically healthy dogs (control) and 133 dogs with CDMD.
Methods: Case-controlled, retrospective study. The angle of tracheal bifurcation (TB angle), ratio of tracheobronchial diameters to thoracic inlet distance (TD/TI) at six locations: cervical, thoracic inlet, thoracic, carina, right and left cranial main stem bronchi (RMB and LMB) were measured on radiographs; diagnosis of CDMD was based on echocardiographic characteristics and categorized based the modified New York heart association (NYHA) functional classification.
Results: The prevalence of TC prior to carina in control and CDMD were 28% and 29%, respectively (P=0.52). No significant differences in the TB angle and TD/TI were found among controls and groups of NYHA I and II; the TB angle, comparing to controls, TD/TI at carina and LMB of groups of NYHA III and IV were significantly different ($P \leq .001$). In CDMD, VHS was negatively correlated to carina/TI, RMB/TI and LMB/TI ($P \leq .002$); and left atrium/aorta root diameter ratio (LA/Ao) was negatively correlated to carina/TI, RMB and LMB/TI ($P \leq .003$). The TB angle was positively correlated to VHS and LA/Ao ($P \leq .009$).
Conclusions: Development TC was not associated with CDMD in dogs. Narrowing of tracheobronchi in CDMD associated with the anatomical regions where directly contacted with the heart. Degree of TBC was associated with severity of CDMD.

Key words: dogs, tracheobronchial diameter, chronic degenerative mitral valvular disease

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Background

Chronic degenerative mitral valvular disease (CDMD) and tracheobronchial collapse (TBC) are two of the most highly prevalent cardiopulmonary diseases in small breed dogs. The high rate of coexistence of two syndromes and similar clinical signs, such as coughing and panting, contributes to the diagnostic and therapeutic dilemma.[1,2] In dogs, CDMD is the most common acquired cardiovascular disease.[3] The prevalence of CDMD is strongly age and breed dependent: approximately 75% in dogs order than 16 years.[3,4] Chronic degenerative mitral valvular disease is characterized by chronic myxomatous mitral valve degeneration resulting in thickening and incomplete apposition of the valve leaflets during systole with secondary mitral valve regurgitation (MR).[5,6] Several complications can occur concomitantly with MR worsening, including left- and then right-sided congestive heart failure secondary to elevated pulmonary artery pressure.[7-10] Clinical signs are associated with the progress of CDMD and resulted from decompensated heart failure.[11]

Tracheobronchial collapse is defined either by narrowing of the lumen of the trachea and bronchi, prolapsed of the dorsal tracheal membrane, or combination of those abnormalities [12]. Tracheobronchial narrowing is a multifactorial process that results from weakening of the tracheobronchial cartilage.[13,14] Many dogs with tracheal collapse (TC) have collapse of both cervical and intrathoracic trachea.[15] When bronchial collapse is found in conjunction with tracheal collapse, this is termed tracheobronchial collapse.[2,16] In some dogs, the principal bronchi are collapsed, with the right and left cranial lobar bronchi affected most commonly.[16] The diagnosis of TBC is made by visual identification of > 25% reduction in luminal diameter of airway during tracheobronchoscopy in dogs.[16,17] Although tracheobronchoscopy has been widely considered as the reference gold standard method for diagnosis and

staging TBC, it requires to be operated under general anesthesia.[18] Thoracic radiographic examination is a routine and essential diagnosis for evaluation of tracheobronchial diameters and cardiac silhouette.[19] The ratio of tracheobronchial diameters to thoracic inlet distance (TD/TI) on thoracic radiographs is a quantitative value for objective estimation of tracheobronchial diameters.[20,21] In dogs with CDMD, the compressed left cranial mainstem bronchus (LMB) and associated clinical signs had been anecdotally attributed to the presence of severe left atrial enlargement.[1,22] Determination of the TD/TI is a convenient and simple measurement for tracheobronchial narrowing and compression by heart in dogs.[20]

The tracheal bifurcation angle (TB angle) is another supportively quantitative measurement to evaluate the enlargement of left atrium and it provide some information of the severity of heart failure in dogs with CDMD.[23,24] Significant differences of the TB angle have also been observed between dogs with normal and increased left atrial size.[23]

Although the high comorbidity was observed between CDMD and TBC in small geriatric dogs, only few studies focused on the cardiac manifestations of respiratory disorders or the inverse relationship in the veterinary literatures and merely a limited population of TBC was included in these studies.[2,25,26]

This study aimed to estimate the prevalence of TBC in dogs with CDMD. The secondary aim of this study was to investigate the airway manifestations of heart failure in dogs with CDMD and to clarify whether a relationship between left atrial enlargement and airway collapse by comparing the angle of tracheal bifurcation and TD/TI ratio in clinically healthy small breed dogs and dogs with CDMD in different stages of heart failure.

Materials and Methods

Animals and clinical evaluation

One hundred eighty-seven client-owned small breed dogs (BW<10 kg) that presented to the National Taiwan University Veterinary Hospital between April 2009 and November 2011 were selected for this study.

Of the 187 dogs, 54 clinically healthy dogs without history of cardiopulmonary diseases were classified as healthy controls (Table 1). The age of these dogs was between 12 months and 8 years. The physical condition was evaluated by annual wellness check-ups and deemed as clinically healthy.

In group of CDMD, 133 dogs were included. The condition of CDMD was diagnosed echocardiographically. Through a medical record of clinical signs, findings of physical examinations and chest radiographs, condition of heart failure of these dogs were further classified based the modified New York heart association (NYHA) functional classification (Table 1).

Complete physical examination, systolic blood pressure measurement, chest radiography, electrocardiography (ECG), and echocardiography (two-dimensional, M-mode, and Doppler) were carried out in all dogs. The owner's consent for each dog was obtained before enrollment in the study.

Thoracic radiographic measurements

All measurements were carried out using electronic calipers of the digital thoracic radiographic system.

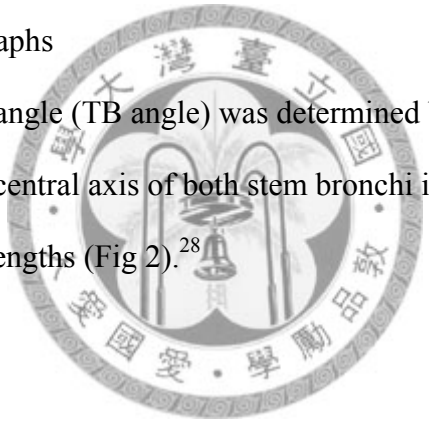
The lateral thoracic radiograph:

1) Vertebral heart scale (VHS) was obtained using the method described by Buchanan and Bücheler. The reference range in this study was 9.2 to 10.2 vertebrae.[27]

2) Ratio of tracheobronchial diameters to thoracic inlet distance (TD/TI): TI was measured from the ventral aspect of the midpoint of the first thoracic vertebra to the dorsal surface of the manubrium at its minimal distance, whereas the tracheobronchial intraluminal diameters (TD) were measured at six locations of trachea and bronchi (cervical, thoracic inlet, thoracic, carina, right and left cranial mainstem bronchi (RMB and LMB) and perpendicularly to the long axis of trachea (Fig 1).[20] In this study, the ratio of TD/TI <0.16 at thoracic inlet, or the narrowest diameter of trachea prior to carina showing TD/TI <0.16 was considered collapsed trachea.[18,20]

The ventral dorsal radiographs

1) Tracheal bifurcation angle (TB angle) was determined by the intersection of lines positioned along the central axis of both stem bronchi in the left and right caudal lung lobs over their lengths (Fig 2).[28]



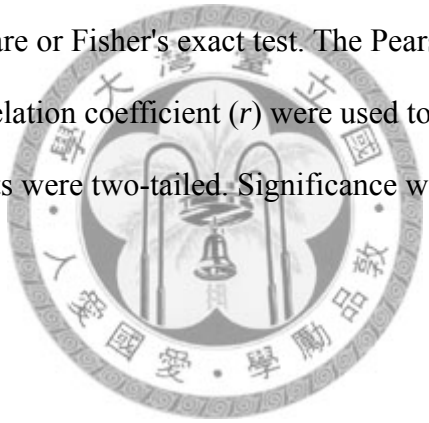
Echocardiography

Echocardiography examinations were performed in conscious status. All dogs were gently restrained in lateral recumbent positions using the 2D-guided M mode with ultrasound units equipped with 2-5 and 5-7.5 MHz transducers[a]. Echocardiographic indices, including the left ventricular dimension at end-diastole (LVEDD) and end-systole (LVESD), the thickness of left ventricular free wall (LVFW) and interventricular septum (IVS) at end-diastole, left atrial/aortic root ratio (LA/Ao), ejection fraction (EF), and fractional shortening (FS), were measured from the standard views obtained from the right parasternal images. The inflow of trans-mitral and trans-tricuspid, the flow of pulmonary artery and aortic flow were measured from the left apical location. Mitral and tricuspid regurgitation were also

evaluated by Doppler-derived echocardiography from the left apical location.

Statistical analysis

Data were expressed as the means ± standard deviations (SDs). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used for testing normal distribution of all data with commercial computer statistic software[b]. Differences in continuous variables between groups were evaluated by one-way analysis of variance (ANOVA), followed if necessary by Student's *t*-test with Bonferroni correction. Where the data were not normal distributed were analyzed by using Kruskal-Wallis test followed by the post-hoc Mann-Whitney U-test. Comparison of frequencies was using the Pearson chi-square or Fisher's exact test. The Pearson product-moment and Spearman rank order correlation coefficient (*r*) were used to assess the relationship between variables. All tests were two-tailed. Significance was defined as *P*-value < .05.



Results

Patient characteristics

A total of 187 dogs of 13 different small breeds were enrolled in this study (Table 1).There was no statistical significance among five groups in sex distribution and body weight, but age of healthy controls was significantly lower compared with dogs affected with CDMD in different modified NYHA classes (*P*< .001) (Table 2).

Thoracic radiographic measurements

Results of the thoracic radiographic measurements are presented in Table 3. In right lateral radiographs, the VHS of group classified IV was significantly higher than healthy controls and groups of NYHA I, II and III (VHS: 12.0±1.2, *P*< .001) and the

VHS of groups NYHA II and III were significantly higher than healthy controls (*P*= .008 and *P*= .002, respectively).

The angle of tracheal bifurcation in NYHA IV group was significantly larger than other groups (TB angle: 93.2±6.4^{o}, *P*< .001) and the angle of NYHA III group (TB angle: 79.0±10.8^{o}) was significantly larger than healthy controls (TB angle: 65.7±8.7^{o}, *P*< .001) and NYHA I group (TB angle: 66.7.0±7.9^{o}, *P*= .005).

The prevalence of collapsed trachea defined at thoracic inlet in healthy controls and dogs affected with CDMD was 22% and 28%, respectively (*P*= .47); whereas the prevalence of collapsed trachea defined at the location prior to carina with TD/TI < 0.16 in healthy controls and dogs affected with CDMD was 28% and 29%, respectively (*P*= .52). No significant differences in the TD/TI of cervical, thoracic inlet, thoracic, carina, right and left main stem bronchi were found among healthy controls, dogs with CDMD categorized in groups of NYHA I and II; whereas the TD/TI at carina and LMB of the dogs with CDMD categorized in group of NYHA III (carica/TI: 0.164±0.051; LMB/TI: 0.078±0.027) and IV (carica/TI: 0.152±0.043; LMB/TI: 0.069±0.022) were significantly different (*P*= .001, *P*< .001, *P*= .001, *P*< .001, respectively) comparing to those of healthy controls.

No significant differences at the six locations of TD/TI of trachea and bronchi were found among the breeds of Chihuahuas, Maltese terriers, Miniature Poodles, Pomeranians, and Yorkshire Terriers of the healthy controls (*P* > .20); and there was no significant correlation between the age of the healthy controls and the TD/TI in the six locations of trachea and bronchi (*P* > .30).

In dog with CDMD, VHS was negatively correlated to carina/TI, RMB/TI and LMB/TI (*r*=-0.29, *r*=-0.31 and *r*=-0.24 respectively; *P*< .001, *P*< .001 and *P*= .002, respectively); and LA/Ao was negatively correlated to carina/TI, RMB and LMB/TI (*r*=-0.39, *r*=-0.48 and *r*=-0.45, respectively; *P*= .003, *P*= .001 and *P*= .001,

respectively). The angle of tracheal bifurcation was positively correlated to VHS and LA/Ao (r=0.26 and r=0.37 respectively; P= .002 and P= .009, respectively).

Echocardiography

Results of the two-dimensional echocardiographic indices are presented in Table 4. The left ventricular diameter and wall thickness, EF and FS were not significantly different among healthy controls and groups of four stages of NYHA classification. However, the left ventricular diameter to aortic root diameter ratio (LVEDD /Ao) of dogs with CDMD categorized in modified NYHA IV was significantly higher as compared with dogs in other groups (P< .003). The LA/Ao of dogs in NYHA IV group was significantly higher than other groups (LA/Ao=2.54±0.37, P< .001). In NYHA III group, the LA/Ao was significantly higher than NYHA I and healthy controls (P= .041 and P= .026, respectively).

In Doppler hemodynamic assessment, no statistical significance of mitral E/A, tricuspid E/A, aortic and pulmonary artery flow velocity was found among healthy controls and dogs in groups of NYHA I to IV. The mitral and tricuspid regurgitation velocity was not significantly different among groups of NYHA I, II, III and IV.

Discussion

Chronic degenerative mitral valvular disease and TBC are common combination in small breed dogs, and the clinical signs of these two conditions are frequently overlapped [2]. Chronic airflow limitation and the reduced lung function had been demonstrated as independently causal factors for cardiovascular diseases in many large-scale epidemiological studies of human patients.[29-31] In this study, the prevalence of TBC was higher in dogs with various severity of CDMD, however no significant difference was found between healthy controls and dogs with CDMD.

Tracheal collapse is common in small breed dog with a prevalence of 0.5 to

2.9%.[32,33] In dogs with respiratory illness, the bronchoscopic prevalence of TBC and bronchial collapse were ranged 21% and 30%, respectively.[16] The radiography have been reported as an effectively diagnostic modality in dogs with TC and collapse of the main bronchi, but the sensitivity and specificity were varied with the position of collapsed trachea and the degree of the dynamic tracheal luminal change during tidal respiration.[19,34] In this study, TC was defined by TD/TI <0.16 radiographically.[18,20] Cases with mild degree of tracheal luminal changes affected by respiratory pattern during the radiographs taken would be underestimated. Nevertheless, the prevalence of TC in clinically healthy dogs and dogs affected with CDMD was higher than the results reported by previous studies. The high prevalence of TC in both groups might simply reflects the popularity of the most predisposed breeds included in this area, such as Maltese terriers, Pomeranian, Yorkshire terrier, Shih Tzu, Chihuahuas, and Miniature Poodle, accounted for 89% of cases in this study.[19,32]

In this study, the TD/TI of cervical, thoracic inlet and thoracic levels were not significantly different between healthy controls and dogs with CDMD at all four NYHA classifications. No statistical correlation was found between the left ventricular echocardiographic indices and the TD/TI of cervical, thoracic inlet, and thoracic levels. These findings suggested that TC was not associated with the higher prevalence and severity of CDMD in small breed dogs. However, TD/TI at carina and LMB in dogs with CDMD categorized in NYHA III and IV was significantly decreased comparing to those of healthy controls. Both VHS and echocardiographic LA/Ao had significantly negative correlations with the carina/TI, RMB/TI and LMB/TI. And the TB angle in the groups of NYHA III and IV was significantly higher than those in the healthy controls. The TB angle was positively correlated to VHS and LA/Ao. Dorsal elevation of the trachea and carina, and dorsal displacement of the left mainstem bronchus by the enlarged left atrium and left ventricle on lateral

radiographs have been widely applied as indicators of CDMD.[22,35-37] Compression of the bronchus in dogs with CDMD was believed to be associated with the enlarged left atrium and the degree of the compression was related to the severity of CDMD in our study.

Bronchoscopic evidence suggested that the left cranial bronchus was the most commonly affected location of bronchomalacia, i.e. bronchial collapse.[16,38,39] Investigation on the development and location of bronchomalacia and in dogs with no/mild and moderate/severe left atrial enlargement caused by CDMD indicated that dorsal and ventral segments of the left cranial lobar bronchus were affected most commonly, followed by the left caudal and right middle lobar bronchi. However, no significant difference in site or severity of airway collapse between dogs affected with no/mild and moderate/severe left atrial enlargement.[2] On the other hand, bronchomalacia has been reported to occur in 87.5% brachycephalic dogs with respiratory distress and noisy breathing, generally at age less than three years. The prevalence of bronchial collapse in brachycephalic breeds has been found to be higher than the prevalence in other breeds (30%).[16,39] Narrowing or compressed left cranial bronchi may also be contributed to other factors, such as ages, body weight, and inflammatory conditions.[38,39] In the present study, there were no significant differences in the TD/TI of trachea and bronchi among the five predisposed breeds in the controls and no significant correlation of the age in the healthy controls. The results in our study indicated that the anatomical link to the heart might be critical in the development of compression of and left bronchus.

There were limitations in our study, no bronchoscopic determinations of tracheobronchial diameters were applied to our dogs, all included dogs were client-owned. The impact of TBC on heart functions may not be entirely elucidated using based conventional assessments of echocardiography, future studies regarding

evaluation of cardiac function using different echocardiographic analysis is warranted in dogs with respiratory disorders.

Conclusions

This study failed to identify an apparent increase in the prevalence of TBC in dogs with CDMD and did not find significant differences of the trachea diameters among healthy controls and dogs with CDMD in groups of NYHA I, II, III and IV despite the high comorbidity was subjectively observed between CDMD and TBC in small breed dogs. These results implied that the CDMD was not associated with TC in dogs. Compression of carina and bronchus in dogs with CDMD only developed where the anatomical regions directly contacted with the heart. Degree of carinal and bronchial compression was associated with severity of CDMD.

Footnotes

[a] MyLab^{TM} 50 Family, Esaote, Genova, Italy

[b] SPSS Version 12.0.1, Lead Technologies Inc., Charlotte, North Carolina, USA

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Table1. Distribution of breeds in clinically healthy small breed dogs and dogs with chronic degenerative mitral valvular disease (CDMD) in different stages of heart failure based on the classification of modified New York Heart Association (NYHA).

Breed	Healthy	NYHA 1	NYHA 2	NYHA 3	NYHA 4
Beagle	0	0	1	1	0
Chihuahua	6	0	3	4	4
French Bulldog	1	0	0	0	0
Maltese terrier	18	9	10	20	5
Miniature Dachshund	1	0	1	2	0
Miniature Pinscher	0	0	1	0	0
Miniature Poodle	6	0	1	4	3
Miniature Schnauzer	2	0	1	1	1
Mongrel	1	1	1	2	0
Pomeranian	8	8	5	6	2
Pug	1	0	0	1	0
Shih Tzu	1	1	12	3	2
Yorkshire Terrier	9	2	5	6	4
Total	54	21	41	50	21

Table 2. Patient characteristics of clinically healthy dogs and dogs with chronic degenerative mitral valvular disease (CDMD) in different stages of heart failure based on classification of the modified New York Heart Association (NYHA).

Indices	Healthy (n=54)	NYHA 1 (n=21)	NYHA 2 (n=41)	NYHA 3 (n=50)	NYHA 4 (n=21)
Age (years)	4.8 ± 2.3	8.9±3.4†	11.8±3.4†	11.4±3.9†	11.2±3.0†
Sex (female/male, %)	48	43	46	46	38
BW (kg)	3.8 ± 2.4	3.6±2.4	3.9±2.0	4.2±2.5	4.3±2.0
HR (beat per minute)	123±35	122±16	128±25	134±25	134±18

Measurements are presented as mean ± SD.

† $P < 0.05$ relative to the healthy group.

Table 3. Results of vertebral heart scale (VHS), tracheal bifurcation angle and the ratio of tracheobronchial diameters to thoracic inlet distance (TD/TI), diameters of six locations of trachea and bronchi (cervical, thoracic inlet, thoracic, carina, right and left main stem bronchi) of clinically healthy small breed dogs (healthy controls) and dogs with chronic degenerative mitral valvular disease (CDMD) in different stages of heart failure based on the classification of modified New York Heart Association (NYHA).

Indices	Healthy (n=54)	NYHA 1 (n=21)	NYHA 2 (n=41)	NYHA 3 (n=50)	NYHA 4 (n=21)
VHS	9.7±0.8	10.2±0.8	10.5±1.1†	10.6±1.0†	12.0±1.2†
Tracheal bifurcation angle^{o}	65.7±8.7	66.7±7.9	71.5±11.3	79.0±10.8†	93.2±12.35†
Portion of Trachea					
Cervical/TI	0.239±0.063	0.247±0.045	0.252±0.067	0.247±0.062	0.234±0.052
Thoracic inlet/TI	0.197±0.052	0.197±0.043	0.200±0.083	0.204±0.049	0.198±0.034
Thoracic/TI	0.205±0.043	0.193±0.030	0.186±0.053	0.192±0.032	0.182±0.045
Carina/TI	0.196±0.057	0.194±0.037	0.180±0.056	0.164±0.051†	0.152±0.043†
Left main stem bronchi/TI	0.098±0.024	0.097±0.027	0.087±0.027	0.078±0.027†	0.069±0.022†
Right main stem bronchi/TI	0.099±0.030	0.097±0.036	0.094±0.027	0.093±0.032	0.073±0.026

Measurements are presented as mean ± SD

† $P < 0.05$ versus corresponding healthy group.

Table 4. Echocardiographic indices in clinically healthy small breed dogs and dogs with chronic degenerative mitral valvular disease (CDMD) in different stages of heart failure based on the classification of modified New York Heart Association (NYHA).

Indices	Healthy (n=54)	NYHA 1 (n=21)	NYHA 2 (n=41)	NYHA 3 (n=50)	NYHA 4 (n=21)
LVEDD (mm)	19.1±4.3	19.8±3.8	21.8±3.9	23.3±2.7	30.2±5.7
LVEDD/Ao	1.41±0.98	1.70±0.33	1.99±0.27	2.02±0.24	2.83±0.43†
LVFWd (mm)	5.4±1.3	6.2±0.7	5.7±1.0	6.1±0.9	5.7±1.1
IVSd (mm)	4.7±0.8	5.7±0.6	6.2±0.8	5.8±0.8	5.8±0.7
EF (%)	74.7±9.4	79.0±6.0	77.8±7.8	79.1±6.1	77.6±6.2
FS (%)	43.1±9.5	45.0±6.0	45.2±7.6	47.3±6.2	47.8±5.5
LA/Ao	1.27±0.25	1.44±0.20	1.53±0.51	1.86±0.18†	2.54±0.37†
Mitral E/A	1.13±0.12	1.08±0.33	1.22±0.31	1.35±0.64	1.56±0.54
Tricuspid E/A	1.03±0.30	1.09±0.46	1.10±0.30	1.16±0.33	1.26±0.52
Aortic flow(m/s)	0.94±0.22	0.83±0.39	0.88±0.34	0.90±0.16	0.98±0.23
Pulmonary artery flow (m/s)	0.77±0.10	0.82±0.32	0.84±0.23	0.81±0.27	0.78±0.10
MR (m/s)	-	1.71±0.98	2.64±1.88	3.35±1.65	4.26±1.37
TR (m/s)	-	1.09±0.50	1.29±1.64	1.39±0.77	2.39±1.13

Indices values are presented as mean ± SD.

EF, ejection fraction; FS, fractional shortening; IVSd, thickness of interventricular septum at end-diastole; LA/Ao, left atrial/aortic root ratio; LVEDD, left ventricular dimension at end-diastole; LVEDD/Ao, left ventricular dimension at end-diastole to aortic root ratio; LVFWd, thickness of left ventricular free wall at end-diastole; Mitral E/A, mitral early diastolic velocity/late diastolic velocity ratio; MR, mitral regurgitation; Tricuspid E/A, tricuspid early diastolic velocity/late diastolic velocity ratio; TR, tricuspid regurgitation.

† $P < 0.05$ versus corresponding healthy group.

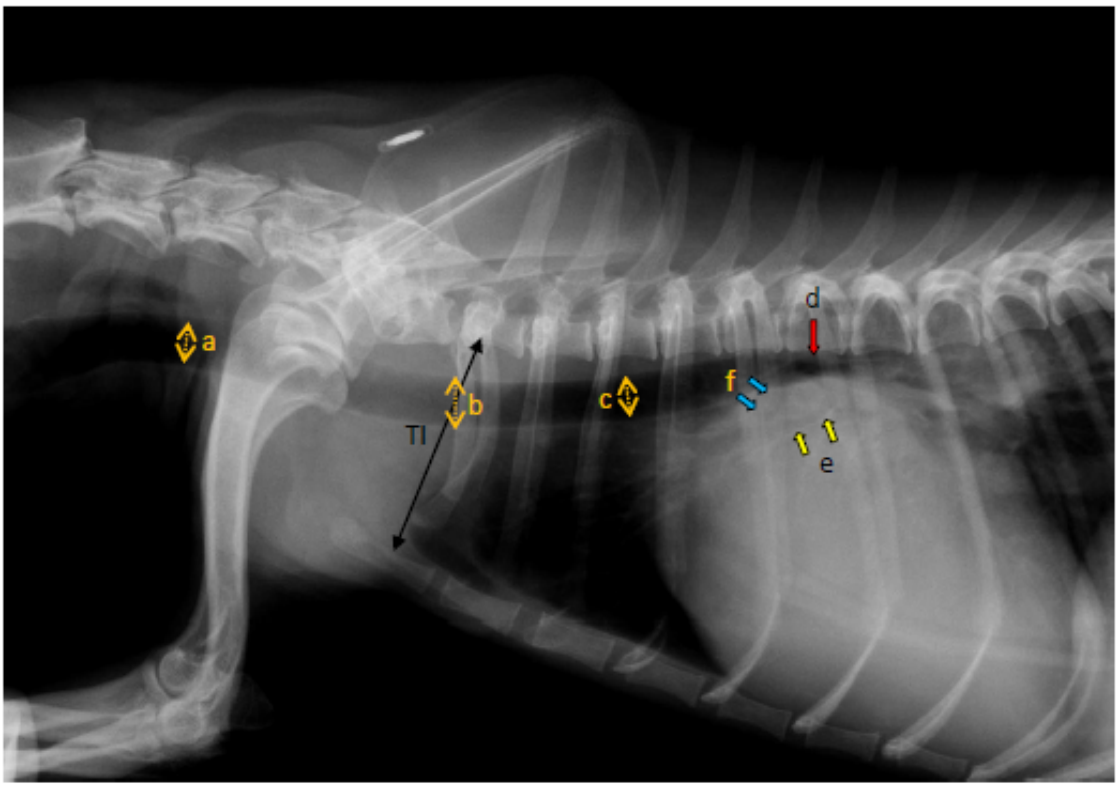


Figure 1 An ensample of the ratio of tracheobronchial diameters to thoracic inlet distance (TD/TI) obtained from a dog with severe chronic degenerative mitral valvular disease classified as NYHA 4, the vertebral heart scale was 12.7, and the left atrium/aorta was 2.6. The tracheobronchial lumen diameters (TD) were measured at six locations of trachea and bronchi: cervical (a), thoracic inlet (b), thoracic, carina (c), right cranial mainstem bronchus (d) and left cranial mainstem bronchus (e).

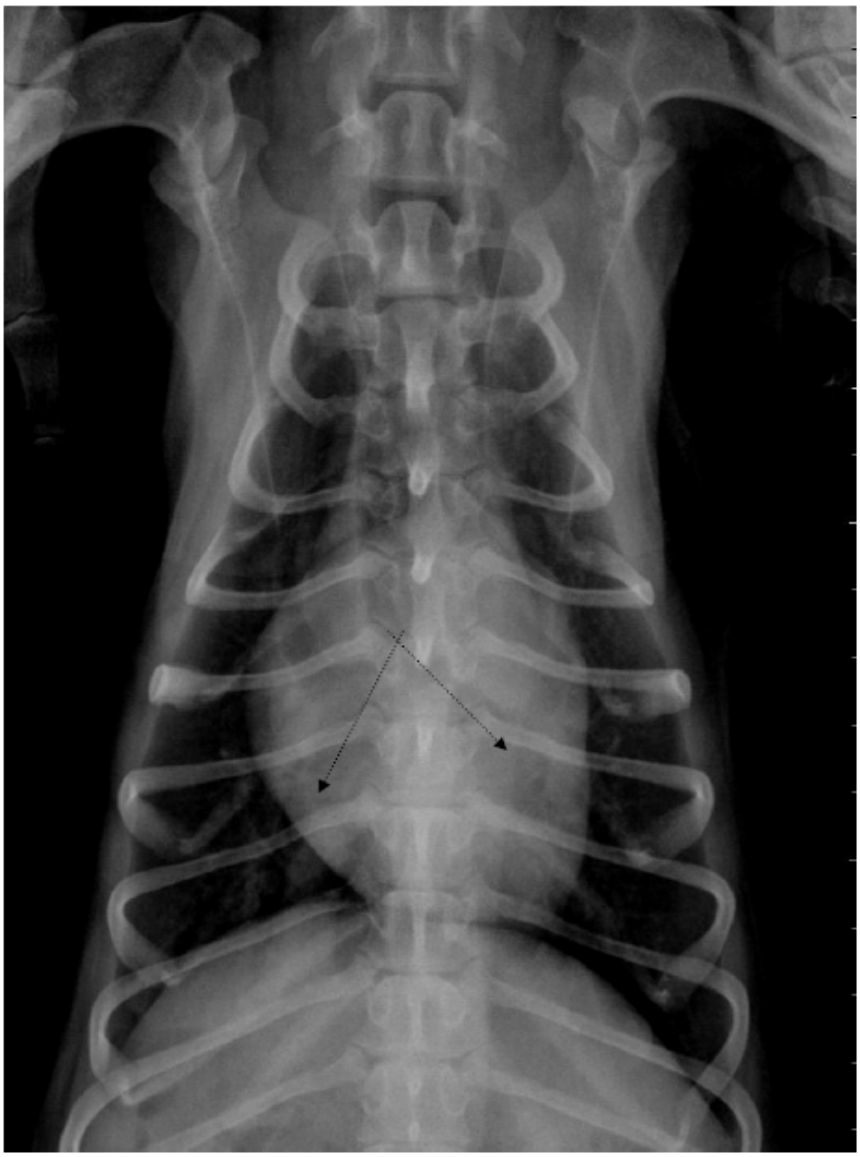


Figure 2 An ensample of the tracheal bifurcation angle obtained from a dog with mild chronic degenerative mitral valvular disease classified as the NYHA 1, the vertebral heart scale was 9.5, and the left atrium/aorta was 1.38. The tracheal bifurcation angle of the dog was 75^{o}.

Chapter 3

Echocardiographic Assessment of Right Heart Indices in Dogs with Elevated Pulmonary Artery Pressure associated with Chronic Respiratory Disorders, Heartworm Disease and Chronic Degenerative Mitral Valvular Disease

Abbreviations:

Ao	aortic root diameter
AT	acceleration time
CDMD	chronic degenerative mitral valvular disease
CV	coefficient of variation
ECG	electrocardiography
EF	ejection fraction
ET	ejection time
FS	fractional shortening
IVS	interventricular septum
LA	left atrial diameter
LVD	end-diastolic left ventricular basal diameter
LVEDD	left ventricular dimension at end-diastole
LV-EI	left ventricular eccentricity index
LVFW	left ventricular free wall
MEA	mean electrical axis
MPA	main pulmonary artery/aortic root diameter ratio
MR	mitral valve regurgitation
PAH	pulmonary artery hypertension
PAP	pulmonary arterial pressure
PH	pulmonary hypertension
PR	pulmonic valve regurgitation
PVR	pulmonary vascular resistance
RV	right ventricular
RVD	end-diastolic right ventricular basal diameter
RVM	right ventricular remodeling
SBP	systemic blood pressure
SPAP	systolic pulmonary artery pressure
TAPSE	tricuspid valve regurgitation, tricuspid annular plane systolic excursion
TR	tricuspid regurgitation
VHS	vertebral heart scale

Echocardiographic assessment of right heart indices in dogs with elevated pulmonary artery pressure associated with chronic respiratory disorders, heartworm disease and chronic degenerative mitral valvular disease

Tzu-Chi Tai, Hui-Pi Huang
Department of Veterinary Medicine, National Taiwan University, Taipei, Taiwan.

Abstract

Background: Elevation of pulmonary arterial pressure (PAP) can be caused by pre- and post-capillary hemodynamic changes. Chronic elevated PAP may lead to right ventricular remodeling (RVM) and right heart failure.

Hypothesis: Different causes of elevated PAP in dogs may lead to diverse RVM.

Animals: 40 clinically healthy dogs and 169 dogs with tricuspid regurgitation.

Methods: Case-controlled, observational study. Dogs were examined and categorized as presenting normal (group 1, n=40); 169 dogs with tricuspid regurgitation (TR >1.5 m/s) were further categorized into group 2 (presented with chronic respiratory disorders and left atrium to aorta ratio (LA/Ao) <1.7, n=33), group 3 (affected with heartworm disease, and LA/Ao <1.7, n=35), group 4 (presented with mild-to-moderate chronic degenerative mitral valvular disease, CDMD, 1.5< LA/Ao ≤ 2, n=61), and group 5 (presented with severe CDMD, LA/Ao > 2, n=40). Right heart indices were measured by the echocardiography.

Results: The ratio of right to left ventricular basal diameter in right ventricular-focused view was significant higher in groups 2 and 3 (P< .002 and P< .001, respectively). The ratio of main pulmonary artery to aortic root diameter, left ventricular compression quantified by eccentricity index were significantly higher in group 3 (P< .008 and P< .001, respectively), and right ventricular acceleration to ejection time was significantly lower (P< .001) in group 3.

Conclusions: Among the three causes of elevated PAP; chronic respiratory disorders and heartworm disease had significant effect on echocardiographic indices of RV. However, right heart indices derived from left heart measurements could be underestimated in dogs with CDMD.

Key words: dog, right heart, pulmonary hypertension, echocardiography.

Part of the study is going to present as a poster in the 22th European College of Veterinary Internal Medicine Congress, Maastricht, Netherlands. Sep. 6-8, 2012.

Introduction

Pulmonary hypertension (PH) is defined as high diastolic or systolic pulmonary arterial pressure and may lead to right ventricular concentric or eccentric hypertrophy, right atrial enlargement, and right-sided heart failure.[1,2] Elevation of PAP above normal constitutes PH and can be caused by pre- and post-capillary hemodynamic changes.[3-5] Pulmonary hypertension is a well-recognized clinical condition in human patients and occurs as a primary or secondary disease of pulmonary vasculature.[6,7] Primary pulmonary artery hypertension (PAH) has been described rarely in dogs.[8] Left-sided heart failure caused by chronic degenerative mitral valvular disease (CDMD), myocardial disease, increased pulmonary blood flow, or increased pulmonary vascular resistance due to conditions such as obstructive pulmonary vascular disease, thromboembolic disease, pulmonary parenchymal disease, or chronic hypoxia are the common secondary causes of PH in dog.[1,9-11] Chronic degenerative mitral valvular may lead to left heart dilation and increased left atrial pressure further causing elevated pulmonary venous pressure (post-capillary PH), pulmonary edema and hypoxia. Reactive pre-capillary PH may occur in the setting of left-heart failure when pulmonary artery vascular narrowing secondary to hypoxia and chronic post-capillary PH.[3] Heart worm disease caused by *Dirofilaria immitis* is the most often reported cause of severe PH in dogs.[12,13] The thromboembolism associated with dead adult worms, chronic inflammation, pulmonary vascular proliferation and dysfunction may cause pre-capillary PH in HWD.[14] Chronic respiratory disorders such as tracheobronchial disease, brachycephalic syndrome and interstitial lung diseases result in chronic hypoxia, mechanical stress and inflammation and may lead to pre-capillary PH.[7,10,15] In human patients with PH, the pathological changes in pulmonary vasculature are characterized by remodeling of small pulmonary arteries due to the proliferation of smooth muscle and endothelia cell, leading to hypertrophy

of media and intima, and formation of plexiform lesions.[14-17] Remodeling of pulmonary vessels leads to restrictions in pulmonary blood flow and progressive elevation in pulmonary vascular resistance (PVR) and PAP.[5,7] Increased afterload resulted from increasing PVR and decreasing pulmonary vascular compliance is the primary cause of right ventricular adaption and ultimately failure in PH.[17,18] Although changes in the pulmonary vasculature are the initial cause of PH, severity of symptoms and survival are strongly associated with right ventricular function, and right heart failure is the main cause of death in human patients with PH.[17]

In recent years, echocardiography allows noninvasive estimates of PAP and evaluation of right heart function and structure.[6,19,20] Doppler echocardiography assessment of tricuspid valve regurgitation (TR) or pulmonic valve regurgitation (PR) can be used to indirectly assess systolic PAP and diastolic PAP, respectively.[1,6] These noninvasive estimates of PAP have been demonstrated to be strongly correlated with invasively measured PAP values in human patients.[19] A number of echocardiographic right heart indices have been show potential prognostic values in human patients with PH, such as pericardial effusion, right atrial size, right ventricular (RV) diameter, tricuspid valve regurgitation, tricuspid annular plane systolic excursion (TAPSE), and eccentricity index.[17] In dogs, several indirect markers of PH have been proposed, including observations of two-dimensional echocardiographic interventricular septal motion, right ventricular and main pulmonary artery size, Doppler derived TR and PR peak velocity, systolic time interval of pulmonary artery flow and RV myocardial velocities measured by tissue Doppler imaging.[6,10,15,20] However, these finding in dogs are usually not quantitative values or only focus on one of PH causes.[1,6,10,21] The quantitative echocardiographic measurements of right heart function and the usefulness of echocardiographic right heart indices as an assessment of right ventricular remodeling (RVM) due to different etiologies of PH are rarely reported in

the veterinary literatures. The aims of this study were to assess the echocardiographic right heart indices among different causes of elevated PAP in dogs.

Materials and Methods

Animals and criteria of inclusion

Medical records of client-owned dogs that echocardiographic examination was performed at the National Taiwan University Veterinary Hospital (NTUVH) between September 2009 and April 2012 were reviewed.

Dogs presented with obvious TR based on color-flow and continuous Doppler examinations were included. Dogs were excluded from this study if evidences of right bundle branch block was evident in electrocardiogram, or primary/secondary lung tumors were detected on chest radiography, or pulmonary stenosis were detected by standard echocardiography.

Forty client-owned clinical healthy dogs that were admitted to the NTUVH for annual wellness checkup during the same period of time were also included as control group (group 1). All these 40 dogs were free from any cardiac or respiratory disorders All dogs, both clinical healthy and diseased dogs included in this study were required to have medical record of complete physical examination, systolic blood pressure measurement, routine blood examination, chest radiography, electrocardiography (ECG), and echocardiography (two-dimensional, M-mode, and Doppler).

Procedures

In this study, the systemic blood pressure (SBP) measurement was measured by a Doppler flow detector by using a 9.5-MHz probe and an inflatable cuff attached to a sphygmomanometer[a]. A standard 6-lead electrocardiogram[b] was recorded in right lateral recumbency. Thoracic radiographic measurements were made using electronic calipers of the digital thoracic radiographic system. Vertebral heart scale (VHS) was

calculated from right lateral recumbent view (Fig 1).[22] Echocardiography examinations were performed in conscious dogs with undergoing continuous ECG monitoring and gently restrained in lateral recumbent positions using the two dimensional (2D)-guided M mode and Doppler mode with ultrasound units equipped with 2-5 and 5-7.5 MHz phased-array transducers[c]. Two-dimensional echocardiographic indices and left heart function assessment, including the left ventricular dimension at end-diastole (LVEDD) and end-systole (LVESD), the thickness of left ventricular free wall (LVFW) and interventricular septum (IVS) at end-diastole, E-point to septal separation (EPSS), ejection fraction (EF) and fractional shortening (FS), and left atrial/aortic root ratio (LA/Ao) were measured from the standard views obtained from the right parasternal images. In this study, left atrial size was categorized depending on the LA/Ao, as normal (LA/Ao < 1.5), mildly (1.5 ≤ LA/Ao ≤ 1.7), moderately (1.7 < LA/Ao ≤ 2), or severely enlarged (LA/Ao > 2).[23] Two-dimensional echocardiographic right heart function assessment, the main pulmonary artery/aorta root ratio (MPA/Ao) was obtained by using the right parasternal transaortic short-axis view. The end-diastolic MPA diameter was measured right under the closed pulmonic valve, the aortic diameter was measured on the same view, and the MPA/Ao ratio was calculated (Fig. 1).[20] The end diastolic and systolic left ventricular eccentricity index (LV-EI) was measured as the ratio of the long axis to short axis diameters of the left ventricle in right parasternal short-axis view at mid-ventricular level (Fig. 2).[24,25] In apical four-chamber view, tricuspid annular plane systolic excursion (TAPSE) was acquired by passing an M-mode cursor through the tricuspid annulus and measuring the distance of annular movement between end-diastole to end-systole (Fig.3).[24,26] The relationship of TAPSE and aortic root diameter (Ao) was estimated by the ratio of TAPSE/Ao. The end-diastolic right to left ventricular basal diameter ratio (RVD/LVD) was defined as ratio of right to left

ventricular basal short-axis dimension in apical four-chamber view with focus on the right ventricle (Fig. 4).[26,27] The RVD/aortic root diameter (RVD/Ao) was also calculated. The diastolic mitral/tricuspid flow velocities, mitral valve regurgitation and the aortic flow were measured from the standard left apical view. The pulmonary flow velocity profile was recorded from the standard right parasternal short-axis view at the basal level. The acceleration time (AT) of the pulmonary outflow was measured from the onset of pulsed Doppler to peak flow. The ejection time (ET) of the pulmonary outflow was measured from the onset to the end of pulsed Doppler flow, and the right ventricular systolic time interval (AT/ET) was then calculated.[10,20] Tricuspid regurgitation and pulmonic regurgitation (PR) were also quantitated by Doppler-derived echocardiography from the standard left apical and right parasternal views. Noninvasive prediction of systolic or diastolic PAP was estimated by application of the modified Bernoulli equation based on the maximal velocity of TR or PR, respectively.[19] In this study, elevated systolic pulmonary artery pressure (SPAP) was defined with affirmative identification of TR velocity > 1.5 m/sec by both color-flow and continuous Doppler modes. TR velocity < 2 m/sec and ≥ 2 to < 3 m/sec was classified as normal-mild and moderate elevated SPAP, TR ≥ 3 m/sec (SPAP > 36 mmHg) was considered as severe PH.[6,20]

Measurement variability

Within-day variability was tested in 6 awake dogs. Repeated image acquisition for the right heart indices was performed in each dog at 3 nonconsecutive time points on a given day. The resulting mean values and standard deviations were used to determine the coefficient of variation (CV).[28]

Statistical analysis

Data were expressed as the means ± standard deviations (SDs). The Kolmogorov-Smirnov test was used for testing normal distribution of all data with commercial computer statistic software[d]. Differences in continuous variables between groups were evaluated by one-way analysis of variance (ANOVA), followed if necessary by Student's *t*-test with Bonferroni correction. Where the data were not normal distributed were analyzed by using Kruskal-Wallis test followed by the post-hoc Mann-Whitney U-test. Receiver operating characteristic (ROC) analysis was used to evaluate the relationship between sensitivity and specificity.[29] The Pearson product-moment and Spearman rank order correlation coefficient (*r*) were used to assess the relationship between variables. All tests were two-tailed. Significance was defined as *P*-value < 0.05.

Results

Cases and Classification

A total of 169 dogs were fulfilled the inclusion criteria and enrolled in this study (Table 1). Tricuspid regurgitation or moderate-to-severe mitral valve regurgitation (MR) was detected during echocardiographic examinations in all these 169 dogs. These cases were further categorized into four different groups based on the etiology of the disorders (Table2):

Group 2: cases of non-cardiac associated chronic respiratory disorders (n=33), all dogs in this group were presented with clinical signs: chronic exercise intolerance, shortness of breath, resting or exercise-induced cyanosis, dry cough, bilateral respiratory crackles, marked diffuse interstitial pulmonary infiltrates on thoracic radiographs. The findings of echocardiographic examinations in these dogs were TR without left sided congestive heart failure.[10] In this group, five dogs with collapsed trachea, five with brachycephalic syndrome, 23 with lower airway diseases.

Group 3: cases of heartworm infestation but without moderate-to-severely enlarged left atrium (n=35). All dogs in this group were positive for circulating antigens of *D. immitis* detected by commercial ELISA kits[e].

Group 4: cases of mild to moderate CDMD and enlarged left atrium ($1.5 \leq$ LA/Ao ≤ 2) with concomitant TR (n=61). Dogs in this group were no evidence of concurrent respiratory tract disease based on thoracic radiographs examination.

Group 5: cases of severe CDMD and markedly enlarged left atrium (LA/Ao > 2) with concomitant TR (n=40). Dogs in this group were no evidence of concurrent respiratory tract disease based on thoracic radiographs examination.

There was no statistical significance among five groups in sex distribution, but age of group1 was significantly lower compared with groups 2, 3, 4 and 5 ($P < .001$). The body weight of groups 2 and 3 was significantly higher compared with groups 1,

4 and 5 (P< .02).

Electrocardiography, Thoracic radiographic measurements

The electrocardiographic parameters: P wave amplitude, duration of P wave and QRS complex, PR and QT interval, mean electrical axis were not significantly different among these five groups. However, the amplitude of R wave in lead II of group 5 was significantly higher than groups 2 and 3 (P< .003) (Table 3).

The mean electrical axis (MEA) in groups 2 and 3 were slightly deviated toward right axis than other groups, however, these were within the reference range.[30,31] Only 21% in group 2, 18% in groups 3, and 9% in group 4 and 3% in group 5 had right axis deviation (MEA > 100^{o}). Overall, the sensitivity of right axis deviated MEA of electrocardiogram to detect moderate-to-severe SPAP (TR > 2.8 m/s) was only 17.2% with a specificity of 92.8%.

The VHS of group 5 was significantly higher than groups 1, 2, 3 and 4 (P< .001), the VHS of group 4 was also significantly higher than group 1 (P< .015).

Echocardiography

Two-dimensional (2D) Echocardiography (left heart function assessment)

Results of the two-dimensional echocardiographic indices are presented in Table 4. The left ventricular diameter and wall thickness, EPSS, EF and FS of groups 1, 2, 3 and 4 were within the reference ranges.[32,33] In group 5, the left ventricular diameter was significantly increased as compared with groups 1, 2, 3 and 4 (P< .001).

Two-dimensional Echocardiography (right heart function assessment)

In group 3, the MAP/Ao and diastolic LV-EI were significantly higher than other groups (P< .008 and P< .001). The RVD/LVD was significantly higher in groups 2

and 3 than groups 1, 4 and 5 ($P< .02$ and $P< .001$) and the RVD/Ao was significantly higher in group 3 than groups 1 and 4 ($P< .019$). There was no statistical significance among 5 groups in systolic LV-EI and TAPSE/Ao (Table 4).

Doppler hemodynamic assessment

In group 1, TR and PR was detected in 3 and 2 dogs, respectively, however, TR and PR was all less than 0.7 m/s.

In group 2, the mean TR velocity was 2.27 m/sec: 44%, 36% and 20% was classified as mild, moderate and severe regurgitation, respectively; and PR was detected in 18 of 33 dogs (mean velocity: 1.2 m/sec, ranged 0.23 to 4.2 m/sec) (Table 2). In group 3, the mean TR velocity was 2.44 m/sec: 24%, 52%, and 24% was classified as mild, moderate and severe regurgitation, respectively; and PR was detected in 20 of 35 dogs (mean velocity 1.33 m/sec, ranged 0.29 to 3.27 m/sec). In group 4, the mean TR velocity was 2.02 m/sec: 50%, 32%, and 16% was classified as mild, moderate and severe regurgitation, respectively; and PR was detected in 15 of 61 dogs (mean velocity 0.84 m/sec, ranged 0.34 to 1.63 m/sec). In group 5, the mean TR velocity was 2.13 m/sec: 64%, 18% and 18% was classified as mild, moderate and severe regurgitation, respectively; and PR was detected in 15 of 40 dogs (mean 0.92 m/sec, ranged 0.26 to 3.23 m/sec).

No significant differences of TR peak velocity and pulmonic regurgitation peak velocity (m/s) were found among groups 2, 3, 4 and 5.

Based on the causes of PAP development in this study, 59.8% (101/169), 20.7% (35/169), 19.5% (33/169) was associated with CDMD, heartworm infestation, and chronic respiratory disorders, respectively.

In group 3, 4 and 5, the mitral regurgitation velocity was significantly higher than groups 1 and 2 (all $P< .001$). The ratio of mitral early and late diastolic peak

velocity (Mitral E/A) in group 5 was significantly higher than groups 2, 3 and 4 ($P < .01$), and the AT/ET of pulmonary artery flow in group 3 was significantly lower than other groups ($P < .001$). There was no statistical significance among 5 groups in tricuspid early and late diastolic peak velocity (Tricuspid E/A), mean aortic and pulmonary flow velocity (Table 5).

The sensitivity to predict elevated PAP was 14% and 54% when AT/ET of pulmonary artery flow was set at ≤ 0.31 and ≤ 0.44, respectively (Table 5)

The correlations of elevated pulmonary artery pressure and electrocardiographic, radiographic, and echocardiographic indices

A significant positive correlation ($P < .05$) was found between SPAP and MAP/Ao, SPAP and RVD/Ao, SPAP and RVD/LVD, whereas a significant negative correlation ($P < .05$) was found between SPAP and AT/ET (Table 6).

The with-in day intra- and inter-observer variabilities of the right heart indices

The with-in day intra- and inter-observer variabilities of the right heart indices are presented in Table7. All CV values of each right heart indices were lower than 16%.

Discussion

Prevalence of PH has been reported in dogs associated with respiratory disorders, HWD, and CDMD ranged 8 to 50%, 6 to 10%, and, 30 to 74%, respectively.[4,6,15,20,34] The severity of systolic PAP estimated based on echocardiographic assessment with respiratory disorders, heartworm infestation and CDMD was classified as mild to moderate in most dogs.[15] In the present study, CDMD also was the most common cause among these three causes of PH in our cases. Similarly, the severity of PH for

most cases among these three causes was classified as mild to moderate. However frequency and severity of heartworm-related PH in this study were higher than the results of previous studies. The difference might be attributed to the high prevalence of *dirofilariasis* in Taiwan.[35,36]

The electrocardiographic changes have been reported in dogs with PH.[6,37,38] These changes were not frequently noted in this study. Although the MEA in dogs with chronic respiratory and heartworm infestation were slightly deviated to right axis than other groups, it was within the reference range. The frequency of right axis deviation was lower than the result of a study that 42% of dogs was experimentally infested with *D. immitis* infestation in the pulmonary arteries.[30] In this study, right axis deviated MEA of electrocardiogram was not sensitive to predict moderate-to-severe elevated SPAP (TR > 2.8 m/s). In dogs with CDMD, the R wave amplitudes in lead I and II were increased significantly compared with dogs with respiratory disorders and HWD. Thus, the MEA could be affected by the left ventricular enlargement.[39] This result agreed with the findings of previous studies that the electrocardiogram is insufficiently sensitive to be a screening tool for detecting significant PH.[6,37]

The echocardiogram is the gold standard for noninvasive method applied in veterinary medicine for diagnosis of PH.[3,38] Measurement of tricuspid valve regurgitation maximal velocity, right ventricular systolic time intervals (AT and ET), and the acceleration time index (AT/ET) had been used to estimate systolic PA pressures.[6,10,20,34,40-42] Values of AT/ET ≤ 0.31 (sensitivity: 73% and specificity: 87%) and ≤ 0.44 (sensitivity: 71% and specificity: 71%) had been used to predict presence of PH, and these values were especially useful to diagnose the PH in dogs without discernable TR or PR.[10,20] In our study, the sensitivity to predict elevated PAP was 14% and 54% when AT/ET was set at ≤ 0.31 and ≤ 0.44, respectively. The

discrepancies between these studies might result from different definition of elevated PAP. Pulmonary hypertension was defined as TR ≥ 3.1m/s and ≥ 2.5m/s in the previous studies, whereas elevated PAP was defined as TR ≥ 1.5 m/s in the present study. Shortened AT or reduced AT/ET may occurs in higher impedance to pulmonary flow with decreased distensibility in the pulmonary vascular bed during early ejection.[10] Lower sensitivity of AT/ET might reflect lower grade TR in our study. Nevertheless the AT/ET of group of heartworm infestation was significantly different from other groups in this study. This suggests differently hemodynamic processes may be developed among these three causes of PH even the PH is mild.

The right ventricle and the pulmonary circulation function as a coupled unit. The non-muscular RV is distensible to generate large amount of blood without causing intraventricular pressure.[18] As pulmonary vascular disease develops, the pulmonary vascular resistance and afterload of RV increases, this further leads to RV systolic and diastolic dysfunction and altered geometry of RV.[6,15,17,27] The contraction of RV is predominantly along the longitudinal plane.[43] TAPSE has proved a useful index for evaluating RV longitudinal function and closely correlates with RV ejection fraction, therefore TAPSE may be applied to evaluate the RV systolic function.[44] Measurement of TAPSE has also been an important prognostic marker in human patients with PH as the TAPSE < 1.8 cm suggesting RV systolic dysfunction.[45] In the present study, TAPSE/Ao was lower in dogs with chronic respiratory disorders and heartworm infestation, however, the difference were not significantly comparing to other groups. This finding might indicate that the chronic respiratory disorders and heartworm infestation associated PH might cause early RV systolic dysfunction compared to with the CDMD associated PH.

In the present study, the MPA/Ao and RVD/Ao were positively correlated to SPAP, and dogs with heartworm infestation had significantly high MPA/Ao and

RVD/Ao ratios compared to other dogs with different causes of PH. *Dirofilaria immitis* and the by-products after infestation direct cause severe intimal proliferation, medial hypertrophy, and thromboembolism of PA.[14,46] This phenomenon is similar to the findings in human patients that the idiopathic, heritable, risk factors induced or associated pulmonary arterial hypertension and chronic thromboembolic PH may cause earlier RV remodeling and dysfunction than those in PH secondary to mitral regurgitation and respiratory diseases.[47,48]

The transpulmonary pressure gradient is proportional to the pulmonary vascular resistance (PVR) as well as the pulmonary artery remodeling and calculated from mean PAP minus mean pulmonary capillary wedge pressure (PCWP).[7] In condition of post-capillary PH, such as left heart diseases, the PAP is elevated proportionally to the elevated mean PCWP and the transpulmonary pressure gradient may be normal or only slightly elevated. After improving the left atrial pressure and PCWP, the PAP could be normalized.[48] Therefore, the pathological changes of pulmonary artery as well as the right heart remodeling in left heart diseases are generally mild compared with the condition of pre-capillary PH in both human and dogs.[3,18,20,48] In the present study, the PAP in conditions of pre-capillary PH (groups of chronic respiratory disorders and heartworm infestation) was generally higher than that of the condition of post-capillary PH (groups of mild-to-moderate and severe CDMD), however the difference was not significant. Nevertheless, the indices of RVM, such as dilated MAP and RVD in condition of pre-capillary PH, were significantly different compared to those in condition of the post-capillary PH. The dogs with severe CDMD exhibited mildly increases in MAP/Ao and RVD/Ao compared to dogs with mild-to-moderate CDMD and healthy controls. These findings suggested the dogs with pre-capillary PH exhibited significant impact on the RVM compared those with PH secondary to post-capillary origins.[4,5,15]

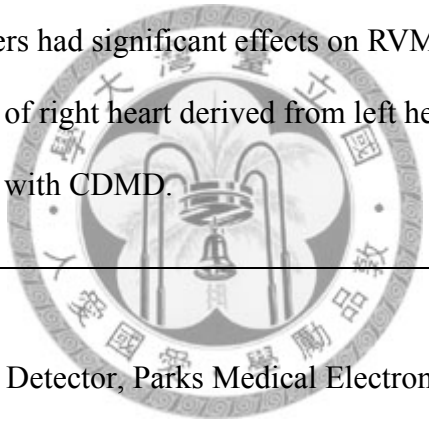
The configuration of the interventricular septum is dependent on the relative pressure gradient between RV and LV at each stage of cardiac cycle.[49,50] When the RV afterload is increased, RV contraction is prolonged and pushing the septum left, and causing the D-shaped short axis LV cavity during this particular period.[51-53] LV compression can be quantified by the eccentricity index and RVD/LVD, which are widely used to assess the interaction of RV and LV and considered abnormal when these ratio are >1 at the end of systole or diastole suggesting RV pressure or volume overload respectively in human patients.[27,52] Both parameters can also be affected by the condition of LV volume or pressure overload.[27,49,54] In the present study, the end-diastolic LV-EI was significantly increased in dogs with heartworm infestation-associated PH compared with those in other groups, and the RVD/LVD in dogs with heartworm infestation and chronic respiratory disorders-associated PH were significant increased compared with dogs with CDMD-associated PH. Similar results were also reported that heartworm infestation and respiratory disorders were the most common causes of RV enlargement and flatten/altered interventricular septum among the etiologies of PH in dogs.[6,15] Nonetheless, the severity of RV pressure and volume overload may be underestimated in dogs with CDMD due to increased LV volume overload.

There were limitations in our study. Firstly, the systolic PAP was estimated noninvasively on the base of peak TR velocity. The method may not always be accurate.[55] In cases with severe PH, the simplified Bernouli equation may underestimate the severity of PH due to the higher RA pressure and the RV systolic dysfunction.[18,26] Secondly, based on a client-owned canine population no corresponding histopathologic assessment was available in this study. Aged small breed dogs are predisposing to development of both CDMD and broncho-interstitial pulmonary disease. The presence of pulmonary edema secondary to CDMD may lead

the broncho-interstitial pulmonary disease undetectable radiographically.[1] Thirdly, TR could be concomitant as apart of degenerative changes of tricuspid valvular disease in aged dogs. Thus, severity of PH based on indirect hemodynamic estimation may be affected.

Conclusion

Right heart indices were affected by chronic respiratory disorders, heartworm disease and moderate to severe CDMD. Based on echocardiographic findings, the severity of RVM was positively correlated with SPAP in general and the process of RVM was affected by the etiologies of PH. Dogs with heartworm infestation and chronic respiratory disorders had significant effects on RVM. However, echocardiographic indices of right heart derived from left heart measurements could be underestimated in dogs with CDMD.



Footnotes

[a] Ultrasonic Doppler Flow Detector, Parks Medical Electronics, Inc., Aloha, Oregon

[b] Cardiovit™AT-1, Schiller AG, Switzerland

[c] SPSS Version 12.0.1, Lead Technologies Inc., USA

[d] IDEXX SNAP®4Dx® Test Kit, IDEXX Laboratories, Inc., USA

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Table 1. Distribution of breeds in clinical healthy dogs (group 1), non-cardiac associated chronic respiratory disorders (group 2), heartworm infestation but without moderate-to-severely enlarged left atrium (group 3), mild to moderate chronic degenerative mitral disease and enlarged left atrium with concomitant tricuspid regurgitation (group 4), cases of severe chronic degenerative mitral disease and markedly enlarged left atrium with concomitant tricuspid regurgitation (group 5)

Breed	All	Group 1	Group 2	Group 3	Group 4	Group 5
Beagle	2	0	0	0	1	1
Bulldog	1	0	0	1	0	0
Cavalier King Charles Spaniel	1	0	0	0	0	1
Chihuahua	9	4	0	0	2	3
Cocker Spaniel	1	0	0	0	1	0
French Bulldog	1	0	0	0	1	0
Fox Terrier	1	0	0	0	1	0
German Shepherd Dog	2	0	0	2	0	0
Golden Retriever	10	1	3	4	1	1
Japanese Chin	1	0	0	0	0	1
Labrador Retriever	2	0	0	1	1	0
Maltese terriers	46	9	4	0	17	16
Miniature Dachshund	12	10	1	1	0	0
Miniature Poodle	12	5	0	0	5	2
Miniature Schnauzer	8	2	1	0	3	2
Mongrel	46	4	9	20	10	3
Papillion	1	0	0	0	0	1
Pekingese	1	0	1	0	0	0
Pomeranian	11	1	3	1	4	2
Pug	4	0	3	1	0	0
Rottweiler	1	0	0	1	0	0
Rough Collie	1	0	0	1	0	0
Shiba Inu	2	0	1	1	0	0
Shih Tzu	17	2	5	0	6	4
Siberian Husky	2	0	2	0	0	0
Welsh Corgi	3	2	0	0	1	0
Yorkshire Terrier	11	0	0	1	7	3
Total	209	40	33	35	61	40

Table 2. Signalment and criteria of categorization of the study, clinical healthy dogs (group 1), non-cardiac associated chronic respiratory disorders (group 2), heartworm infestation but without moderate-to-severely enlarged left atrium (group 3), mild to moderate chronic degenerative mitral disease and enlarged left atrium with concomitant tricuspid regurgitation (group 4), cases of severe chronic degenerative mitral disease and markedly enlarged left atrium with concomitant tricuspid regurgitation (group 5)

Indices	Group 1	Group 2	Group 3	Group 4	Group 5
N	40	33	35	61	40
Age (years)	3.6±2.4	9.3±4.2†	8.5±4.3†	11.3±3.4†	12.0±3.0†
Sex (female/male,%)	54	45	44	45	53
BW (kg)	7.1±5.7	12.9±9.3†	20.2±10.9†	7.2±1.9	5.7±1.8
LA/Ao	1.36±0.08	1.46±0.11	1.43±0.09	1.60±0.25†	2.46±0.18†
TR (m/s)	-	2.27±0.43	2.44±0.35	2.01±0.29	2.13±0.45
Mild TR[a] (%)	-	44	24	50	64
Moderate TR[a](%)	-	36	52	32	18
Severe TR[a](%)	-	20	24	16	18
PR (m/s)	-	1.20±0.44	1.33±0.94	0.84±0.31	0.92±0.39
PR[a](%)	-	55	57	25	38

[a] Frequency.

† $P < 0.05$ relative to group 1.

Table 3. Parameters of electrocardiographic (ECG) in lead II, and chest radiographic measurements in clinical healthy dogs (group 1), non-cardiac associated chronic respiratory disorders (group 2), heartworm infestation but without moderate-to-severely enlarged left atrium (group 3), mild to moderate chronic degenerative mitral disease and enlarged left atrium with concomitant tricuspid regurgitation (group 4), cases of severe chronic degenerative mitral disease and markedly enlarged left atrium with concomitant tricuspid regurgitation (group 5)

Indices	Group 1	Group 2	Group 3	Group 4	Group 5
ECG findings					
P wave height (mV)	0.25±0.11	0.24±0.08	0.26±0.14	0.27±0.12	0.32±0.13
P wave width (ms)	44.5±17.3	47.1±13.1	47.6±21.7	45.6±9.9	44.8±14.0
QRS height (mV)	1.96±0.74	1.43±0.84	1.48±0.79	2.13±1.14	2.55±1.00
QRS width (ms)	56.2±13.0	49.9±10.6	64.5±32.2	45.9±10.1	54.5±23.4
PR interval (ms)	91.7±47.6	111.2±83.6	106.6±43.9	122.6±47.0	103.4±61.7
QT interval (m/s)	203.7±45.6	202.7±34.0	209.3±18.6	193.8±36.3	190.5±25.0
MEA	52.2±22.4	69.2±24.2	57.4±22.7	45.5±12.6	43.1±32.9
Radiographic measurements					
VHS	9.69±0.69	10.32±0.78	10.44±0.84	10.52±1.01†	12.7±1.69†
VHS >10.5 (%)	10	40	43	43	90

Indices values are presented as mean ± SD.

MEA: mean electrical axis; VHS: vertebral heart scale.

† $P < 0.05$ relative to group 1.

Table 4. Echocardiographic indices of left and right heart in clinical healthy dogs (group 1), non-cardiac associated chronic respiratory disorders (group 2), heartworm infestation but without moderate-to-severely enlarged left atrium (group 3), mild to moderate chronic degenerative mitral disease and enlarged left atrium with concomitant tricuspid regurgitation (group 4), cases of severe chronic degenerative mitral disease and markedly enlarged left atrium with concomitant tricuspid regurgitation (group 5)

Left heart indices	Group 1	Group 2	Group 3	Group 4	Group 5
LVEDD (mm)	22.8±6.1	28.8±8.6	34.5±10.8†	26.2±7.8	30.5±7.5†
LVFWd (mm)	6.2±1.7	7.9±2.4†	8.0±1.6†	6.1±1.5	5.3±1.7
IVSd (mm)	6.1±1.6	8.2±2.2†	8.7±2.1†	6.8±1.3	5.5±1.9
EF (%)	75.2±14.7	72.4±10.1	71.8±9.0	77.0±9.6	80.8±9.3
FS (%)	44.3±6.8	41.0±8.7	41.3±8.4	45.1±8.9	50.0±8.5
Right heart indices					
MPA/Ao	1.00±0.06	1.05±0.13	1.17±0.17†	1.02±0.05	1.05±0.06
End diastolic LV-EI	1.02±0.04	1.08±0.12	1.41±0.25†	1.04±0.05	1.00±0.07
End systolic LV-EI	1.04±0.05	1.07±0.11	1.12±0.18	1.02±0.08	1.06±0.05
TAPSE/Ao	0.90±0.21	0.72±0.16	0.84±0.42	0.92±0.24	1.07±0.45
RVD/LVD	0.62±0.10	0.78±0.19†	0.84±0.23†	0.60±0.09	0.56±0.11
RVD/Ao	1.08±0.27	1.28±0.35	1.40±0.25†	1.10±0.24	1.15±0.48

Indices values are presented as mean ± SD.

EF: ejection fraction; EPSS: E-point to septal separation; FS: fractional shortening; IVSd: thickness of interventricular septum at end-diastole; LA/Ao: left atrial/aortic root ratio; LVEDD: left ventricular dimension at end-systole; LV-EI: left ventricular eccentricity index; LVFWd: thickness of left ventricular free wall at end-diastole; MPA/Ao: main pulmonary artery/aorta root ratio; RVD/Ao: right ventricular basal diameter to aortic root diameter ratio; RVD/LVD: right to left ventricular basal diameter ratio; TAPSE: tricuspid annular plane systolic excursion.

†$P < 0.05$ relative to group 1.

Table 5. Doppler-derived echocardiographic indices in clinical healthy dogs (group 1), non-cardiac associated chronic respiratory disorders (group 2), heartworm infestation but without moderate-to-severely enlarged left atrium (group 3), mild to moderate chronic degenerative mitral disease and enlarged left atrium with concomitant tricuspid regurgitation (group 4), cases of severe chronic degenerative mitral disease and markedly enlarged left atrium with concomitant tricuspid regurgitation (group 5)

Indices	Group 1	Group 2	Group 3	Group 4	Group 5
MR (m/s)	1.00±0.39	1.91±0.58	3.79±0.90†	3.84±1.75†	4.67±1.02†
Mitral E/A	1.33±0.16	1.11±0.11	1.17±0.14	1.10±0.11	1.76±0.50
Tricuspid E/A	1.29±0.16	1.11±0.14	1.22±0.18	1.13±0.19	1.15±0.28
Aortic flow (m/s)	0.85±0.09	0.96±0.14	0.99±0.13	0.81±0.10	0.77±0.09
Pulmonary artery flow (m/s)	0.77±0.08	0.89±0.13	0.85±0.07	0.75±0.13	0.72±0.09
Pulmonary artery AT/ET	0.46±0.06	0.44±0.09	0.34±0.09†	0.45±0.08	0.46±0.07
Pulmonary artery AT/ET <0.31 (%)	-	6	42	4	-
Pulmonary artery AT/ET <0.44 (%)	35	47	81	46	39

Indices values are presented as mean ± SD. AT/ET: acceleration time/ejection time of pulmonary artery flow; Mitral E/A: mitral early diastolic velocity/late diastolic velocity ratio; MR: mitral regurgitation; Tricuspid E/A: tricuspid early diastolic velocity/late diastolic velocity ratio.

† $P < 0.05$ relative to group 1.

Table 6. Results of correlation analysis of systolic pulmonary artery pressure (SPAP) and right heart echocardiographic indices in 209 dogs in which SPAP was assessed by Doppler examination

Independent variable	r	*P*-value
MEA	0.134	0.154
MPA/Ao	0.388	0.002
End diastolic LV-EI	0.116	0.344
End systolic LV-EI	0.167	0.233
TAPSE/Ao	0.090	0.629
RVD/LVD	0.283	0.016
RVD /Ao	0.261	0.036
AT/ET	-0.339	0.003

AT/ET: acceleration time/ejection time of pulmonary artery flow; LV-EI: left ventricular eccentricity index; MEA: mean electrical axis; MPA/Ao: main pulmonary artery/aorta root ratio; RVD/Ao: right ventricular basal diameter to aortic root diameter ratio; RVD/LVD: right to left ventricular basal diameter ratio; r, coefficient of correlation; TAPSE: tricuspid annular plane systolic excursion

Table 7. Coefficient of variation (CV) for intra- and inter-observer within-day right heart indices in 6 healthy dogs (CV values are presented as median and range)

Right heart indices	Intra-observer CV (%)	Inter-observer CV (%)
Ao	5.37 (3.37-8.02)	3.49 (1.57-5.69)
MPA	3.60 (2.45-8.35)	3.27 (0.51-10.06)
MPA/Ao	3.49 (1.85-5.71)	2.14 (0.85-7.29)
End diastolic LV-EI	2.93 (1.54-13.64)	2.66 (0.99-4.73)
End systolic LV-EI	3.26 (1.70-5.44)	1.70 (0.94-2.44)
TAPSE	6.73 (4.21-11.96)	8.43 (6.20-13.69)
TAPSE/Ao	8.61 (2.25-15.11)	11.95 (1.60-15.20)
RVD	10.03 (3.32-11.71)	2.08 (0.01-3.97)
LVD	5.53 (2.04-8.60)	2.24 (0.30-3.78)
RVD/LVD	4.99 (3.51-7.37)	1.70 (0.51-3.65)
RVD/Ao	10.88 (7.33-15.03)	5.09 (0.58-12.41)
Pulmonary artery AT/ET	7.16 (1.70-15.86)	3.40 (0.01-8.61)

Ao: aorta root diameter, AT/ET: acceleration time/ejection time of pulmonary artery flow, LVD: left ventricular basal diameter, LV-EI: left ventricular eccentricity index; MPA: main pulmonary artery diameter, RVD: right ventricular basal diameter, TAPSE: tricuspid annular plane systolic excursion.

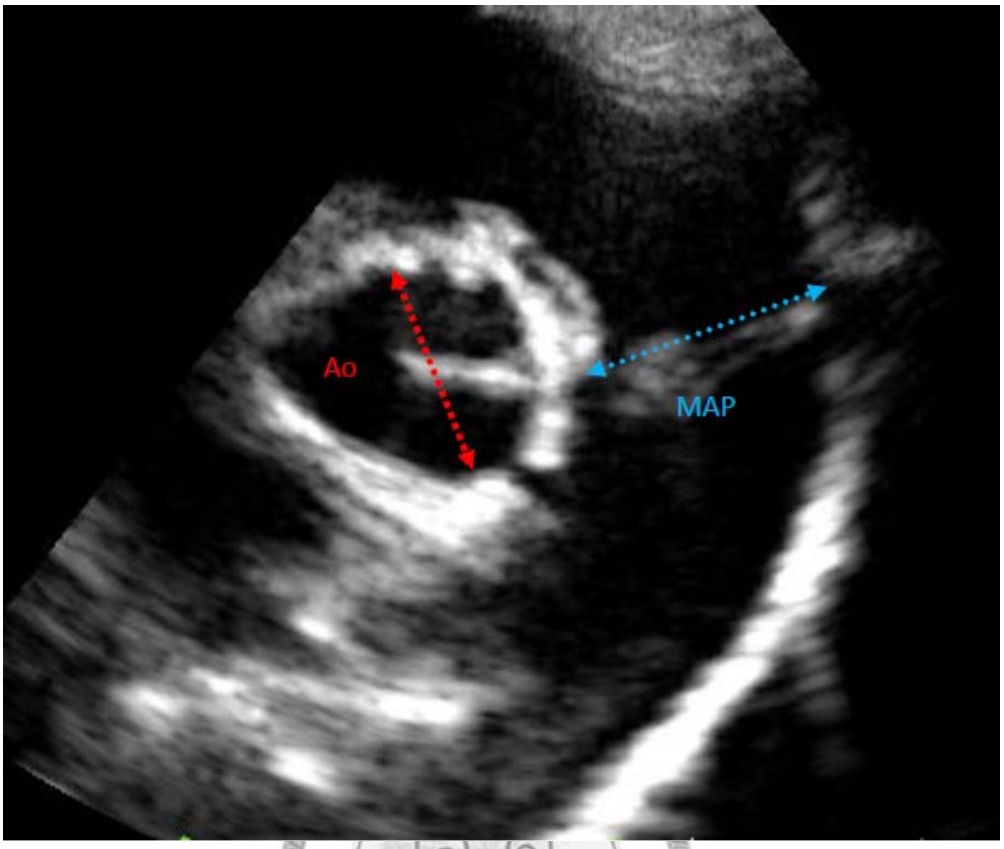

Figure 1 An example of the main pulmonary artery/aortic root diameter ratio (MPA/Ao) obtained from a dog affected by heartworm disease.

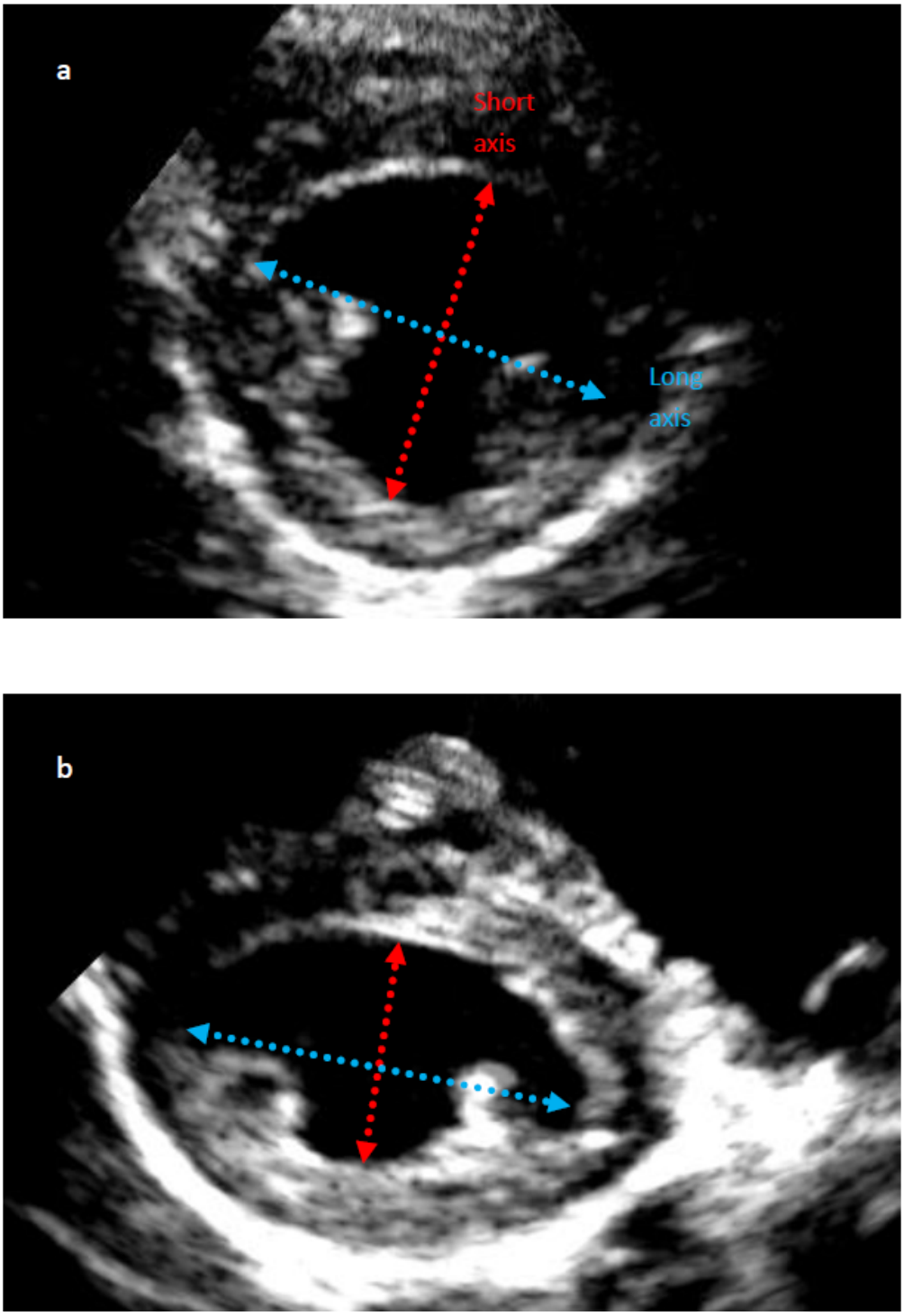

Figure 2 Examples of the end diastolic left ventricular eccentricity index (LV-EI) from a healthy individual (a) and a dog affected by heartworm disease (b).

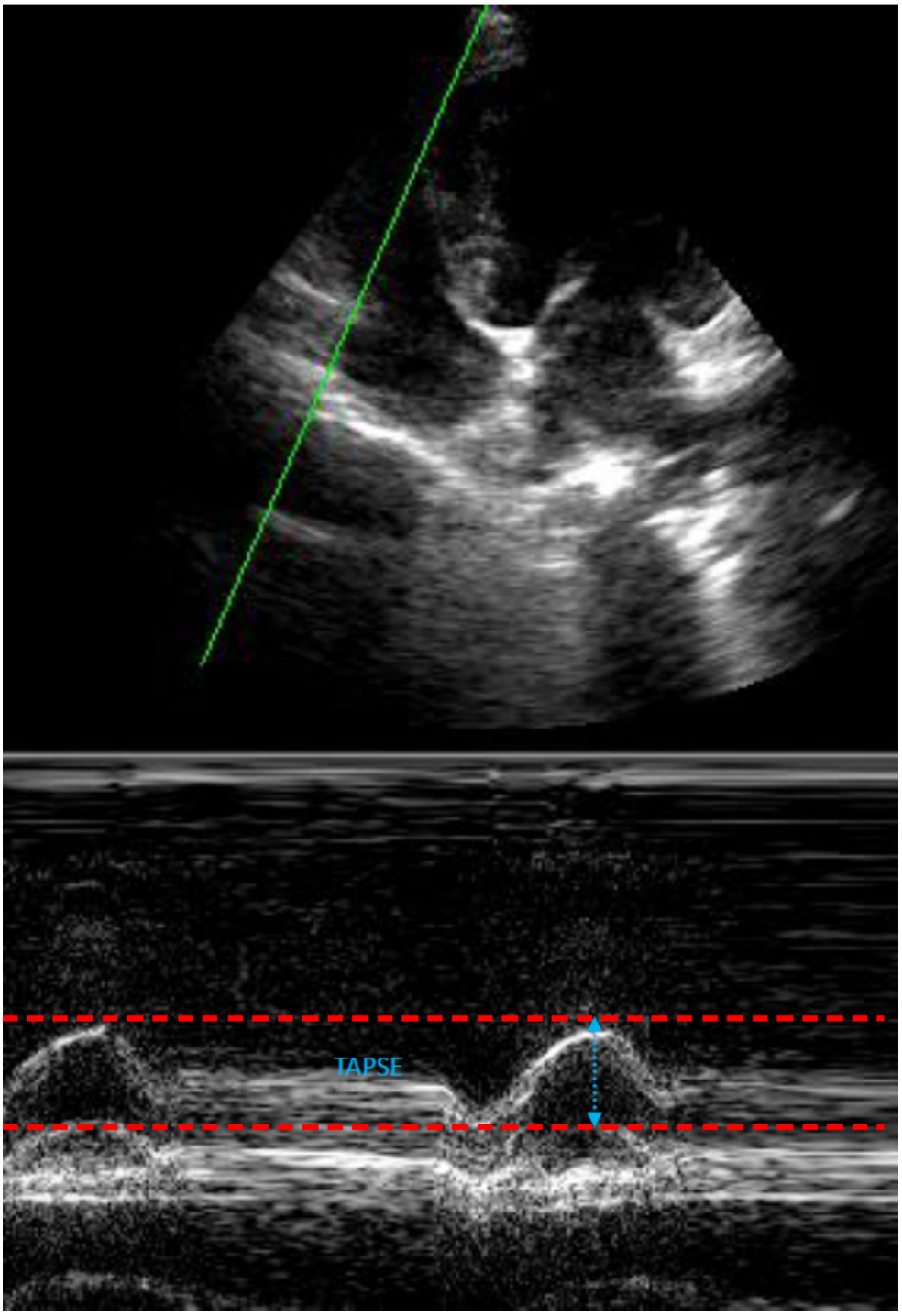

Figure 3 An example of the tricuspid annular plane systolic excursion (TAPSE) obtained from a healthy dog.

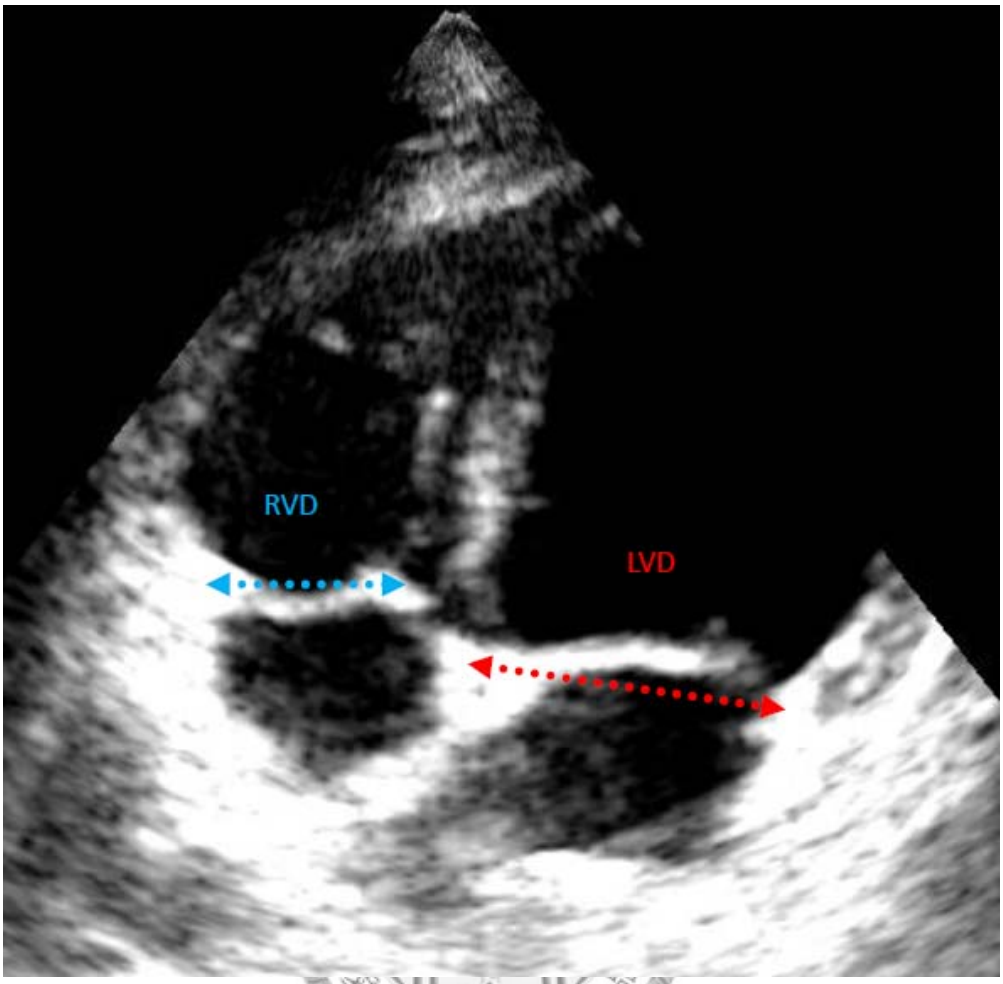

Figure 4 An ensample of the end-diastolic right to left ventricular basal diameter ratio (RVD/LVD) obtained from a dog affected by mild-to-moderate chronic degenerative mitral valvular disease.

Chapter 4

Summarized Discussion

Abbreviations:

CDMD	chronic degenerative mitral valvular disease
HWD	heartworm disease
NYHA	modified New York heart association functional classification
PH	pulmonary hypertension
TBC	tracheobronchial collapse
TD	tracheobronchial diameter
TI	thoracic inlet distance

The respiratory and cardiovascular systems function as a coupled unit. The left heart receives blood from the pulmonary circulation and ejects blood into the systemic circulation; the right heart receives blood from the systemic circulation and ejects blood into the pulmonary circulation.[1] As a result, alterations of the pulmonary vascular resistance and compliance resulted from several pathogenic conditions may change the afterload and preload of the right and left heart.[1-3] In addition to the hemodynamic changes of pulmonary circulation, the other possible pathogenesis of cardiac remodeling in respiratory system disorders include systemic inflammation, oxidative stress, hypoxia, activation of the sympathetic nervous system.[4,5]

Chronic left heart diseases may lead to the increased left atrial and pulmonary wedge capillary pressure.[6] The enlarged left atrium and the elevated pressure in pulmonary vascular bed may result in the anatomic compression of respiratory tract, pulmonary edema, or pulmonary hypertension.[6-9] The pulmonary vascular structural and functional changes resulted from chronic hypoxia, inflammation, direct occlusions or damages caused by chronic pulmonary edema, respiratory tract disorders, or parasitic infestation may lead to the elevated pulmonary vascular resistance, pulmonary artery hypertension, and then right heart failure.[10-14] The left heart may also be affected by the uncompensated right heart due to the phenomenon of ventricular interdependence.[15,16]

Fifty-four clinically healthy small breed dogs and 133 dogs with Chronic degenerative mitral valvular disease (CDMD) in different condition of modified New York heart association (NYHA) functional classification joined in the first study to determine the relationship between tracheobronchial collapse (TBC) and CDMD. In this study, the ratio of tracheobronchial diameters to thoracic inlet distance (TD/TI), diameters at six locations of trachea and bronchi and the angle of tracheal bifurcation were measured on thoracic radiographs. The result presented that the enlarged left

atrium secondary to CDMD might result in the anatomical compression of the trachea and bronchus; however, the study failed to identify that trachea collapse is one of the risk factors for the development of CDMD and left heart failure. In the second study, several right heart echocardiographic indices were measured from 40 clinically healthy dogs and 169 dogs with elevated pulmonary artery pressure resulted respectively from respiratory disorders, heartworm disease (HWD) and CDMD. The chronic respiratory disorders, HWD and CDMD leading to the pulmonary vascular resistant and hemodynamic changes are three of the well recognized etiologies of pulmonary hypertension (PH) in dogs.[13,17-19] As the pulmonary pressure overload persists, the inability of the right ventricle to cope with the elevated resistant results in a vicious cycle of right ventricular dilation and deformation.[13,17,20] The results of this study indicated right ventricular remodeling were affected by the chronic respiratory disorders, HWD, and moderated to severe CDMD. Although the CDVD was the most common cause among these three causes of PH in this study, the pulmonary vascular and right ventricular adaptation were more obvious in dogs with heartworm infestation and chronic respiratory disorders. The different ventricular interdependence among the three causes of PH might be attributed to the interaction between the dilated right ventricle and the different conditions of left ventricle.[15,21]

The respiratory system diseases of dogs might result in different cardiac manifestations. Based on the findings of our studies, the pulmonary vascular remodeling due to the respiratory tract disorders, HWD, and CDMD leaded to the right ventricular adaptation and altered of the patterns of ventricular interdependence. The respiratory tracts were anatomically compressed by the enlarged left atrium caused by CDMD. However, the left ventricle adaptation in respiratory system diseases of dogs still needed to investigate in further study.

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