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Chapter

Echocardiographic Features in Canine Myxomatous Mitral Valve Disease: An Animal Model for Human Mitral Valve Prolapse

Sang-Il Suh, Ta-Li Lu, Ran Choi and Changbaig Hyun

Abstract

Myxomatous mitral valve disease (MMVD) is the most common heart disease in dogs and has many similarities to human mitral valve prolapse (MVP). Transthoracic echocardiography is a non-invasive method for making a diagnosis and predicting the progression of heart failure (HF) in dogs and humans with mitral regurgitation (MR). It enables clinicians to detect the mitral valve (MV) lesions, to evaluate MR severity, and to assess its impact on cardiac remodeling, myocardial function, left ventricular (LV) filling pressures, as well as pulmonary arterial pressure. Furthermore, advanced ultrasound technologies such as tissue Doppler imaging (TDI), strain and strain rate imaging, and two-dimensional (2D) speckle tracking echocardiography (STE) provide a better assessment of global and regional myocardial function. Although the severity of MR and HF in dogs with MMVD is being evaluated as similar to human cardiology, the veterinary cardiologists are more focused on the severity of cardiac remodeling and cardiac dysfunction caused by MR, because surgical restoration of defected mitral apparatus is rarely done in dogs. The chapter will review conventional echocardiographic features of MMVD in dogs to provide a better understanding of the similarities and discrepancies between canine MMVD and human MVP to veterinary and human cardiologists and researchers.

Keywords: mitral valve prolapse, myxomatous mitral valve disease, mitral valve insufficiency, heart failure, mitral regurgitation

1. Introduction

Myxomatous mitral valve disease (MMVD) accounts for 75–80% of heart diseases in dogs and is more prevalent in small and elderly dogs [1, 2]. Due to similarities to human mitral valve prolapse (MVP), it gains huge interest in veterinary and human cardiologists. MMVD and MVP are characterized by progressive myxomatous degeneration of atrioventricular valves and subsequent mitral regurgitation (MR) [3], causing left atrial (LA) and left ventricular (LV) volume overload and left-sided congestive heart failure (CHF) [4]. Although there are many similarities in both diseases (e.g. macroscopic and microscopic pathology, strong genetic background, marked effect of age on prevalence and severity, slow

progression), discrepancies in these two diseases (e.g. much more prevalent in dogs than in humans, less prone to develop endocarditis in dogs, less prominent systolic clicks in dogs) exist [5].

Although there are many diagnostic methods for MMVD, the standard transthoracic echocardiographic examination is a gold standard test for diagnosis and prognosis of MMVD and MVP in dogs and humans, respectively. The echocardiography is non-invasive and enables the clinicians to detect the mitral valve (MV) lesions, to evaluate MR severity, and to assess its impact on cardiac remodeling, myocardial function, left ventricular filling pressures, as well as pulmonary arterial pressure [6–11]. However, conventional ultrasound imaging modalities such as two-dimensional (2D), M-mode, color Doppler, pulse-wave (PW), and continuous-wave (CW) Doppler echocardiography may not be enough to precisely evaluate the severity of mitral valve diseases and to monitor disease progression. Advanced ultrasound technologies such as tissue Doppler imaging (TDI), strain and strain rate imaging, and two-dimensional speckle tracking echocardiography (STE) gain popularity in veterinary and human cardiologists because these technologies can assess and monitor global and regional myocardial function more precisely [12], although those require more expensive ultrasound machine and training.

Human MVP causing MR is divided into two groups: primary (i.e. structural intrinsic valvular disease) and secondary (i.e. nonstructural functional MR caused by non-mitral valve diseases). Like dogs, causes of primary MR are degenerative diseases on the mitral valve, such as Barlow, fibroelastic degeneration, Marfan, Ehlers-Danlos, and annular calcification, although rheumatic disease and toxic valvulopathy can also cause MR in humans [13]. Severity of MR in humans is graded qualitatively (e.g. mitral valve morphology, color flow MR jet, flow convergence zone, CW signal of MR jets), semi-quantitatively (e.g. vena contracta [VC] width, pulmonary vein flow, mitral inflow, TVI mit/TVI Ao), and quantitatively (effective regurgitant orifice area [EROA], regurgitant volume [R Vol]) [13]. LV and LA size and the systolic pulmonary arterial pressure are also used to determine the severity of CHF caused by MR.

Although the severity MR and CHF in dogs with MMVD are being evaluated as similar to human cardiology, the veterinary cardiologists are more focused on the severity of cardiac remodeling (e.g. LA and LV dilation) and cardiac dysfunction caused by MR, because surgical restoration of defected mitral apparatus is rarely done in dogs. Therefore, the echocardiographic indices related to MR severity (e.g. MV morphology, flow convergence zone) are not routinely assessed in dogs with MMVD.

The chapter reviews conventional echocardiographic indices being used for diagnosis and prognosis of canine MMVD to provide a better understanding of the similarities and discrepancies between canine MMVD and human MVP to veterinary and human cardiologists and researchers.

2. Assessment of MR severity

Echocardiography is a gold standard test in the assessment and management of humans and dogs with MR. Although color flow MR jets and CW signal of MR jets are useful for detecting MR, a more quantitative approach is required for determining the severity of MR in humans and dogs.

2.1 Semi-quantification of MR

Although quantitative assessment of MR (e.g. EROA and R Vol) is being used for grading the severity of MR in humans [13], it is rarely used in canine practice,

because it requires more time-consuming interrogation and is often hard to define the location of EROA and flow convergence shape in dogs with MR [14]. Therefore, canine study, especially in practice, focuses more on the semi-quantification of MR (e.g. the maximal ratio of the regurgitant jet area signal to LA area [ARJ/LAA ratio] and vena contracta).

The ARJ/LAA ratio can be easily obtained with the color Doppler imaging (CDI) method and showed good repeatability and reproducibility in dogs [15, 16]. MR can be graded as mild (<30%), moderate (30–70%), or severe (>70%), based on the ARJ/LAA ratio on the CDI study in dogs with MMVD (**Figure 1A**) [15, 16]. Unfortunately, the ARJ/LAA ratio can be affected by many intrinsic factors (e.g. SAP, LA pressure, the spatial orientation of MR jet) and extrinsic factors (e.g. pulse repetition frequency and gain settings) [17]. Several studies found the ARJ/LAA ratio was not closely correlated with the severity of MMVD in dogs, especially in dogs with American College of Veterinary Internal Medicine (ACVIM) B2 and C [18, 19].

The vena contracta is the narrowest width of the MR jet that occurs at or just downstream from the regurgitant orifice and can reflect the severity of MR (obtained from measuring the regurgitant orifice size by the CDI study) (**Figure 1B**) [17]. Although it requires less time-consuming interrogation and is technically easier to obtain, this method is prone to errors, especially in dogs having dynamic regurgitant orifices [14]. Several studies found the VC and VC-derived variables were closely correlated with the severity of MR and survival time in dogs with MMVD [20–22]. One study found the mean (±SD) diameter of the mitral regurgitation vena contracta in a right parasternal long-axis (RPLx) view (VC_R:Ao) and a left apical four-chamber view (VC_L:Ao) indexed to aortic diameter were 0.21 ± 0.14 and 0.24 ± 0.12, respectively, in dogs with MMVD [21]. Furthermore, the VC_L:Ao > 0.24 was closely correlated with survival time (hazard ratio 4.87) [21].

2.2 Quantification of MR

The measurement of the flow convergence area by proximal isovelocity surface area (PISA) is a gold standard method to quantify the MR jet in humans [13]. Although one study found the PISA method was repeatable and reproducible in awake dogs [16], it is more time-consuming and requires several precautions to obtain the optimal acquisition of the flow convergence images in dogs with MMVD [14]. The regurgitation fraction (RF) obtained by the PISA can be used for

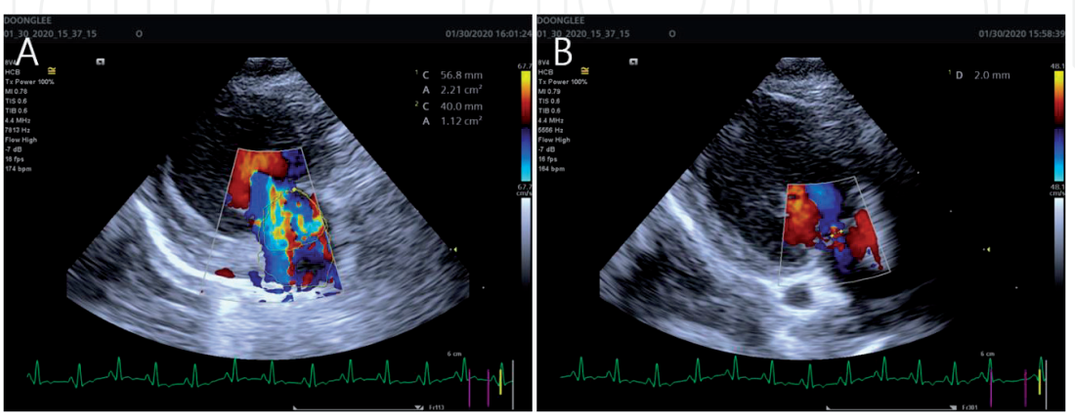


Figure 1.
(A) Semi-quantification of mitral regurgitation (MR). The maximal ratio of the regurgitant jet area signal to the left atrial area (ARJ/LAA ratio) was obtained from a left apical four-chamber view. The ARJ (1.12 cm^2)/ LAA (2.12 cm^2) of this case was 53%, indicating moderate MR. (B) the vena contracta diameter from a left apical four-chamber view (VC_L) was measured as the diameter of the narrowest point of the mitral regurgitation jet, downstream of the region of proximal flow convergence.

determining the severity of MR in dogs (e.g. mild if <30%, moderate if 30–75%, and severe if >75% of RF). Several studies found the RF was closely correlated with the severity of MMVD and other echocardiographic variables (e.g. LA/Ao and systolic PA pressure) [16, 23, 24]. However, one study found the MR quantification of the PISA method showed a wide range of RF (~33% asymptomatic MMVD dogs had moderate to severe RF) and thus is not routinely done in canine practice [16].

3. Assessment of left heart remodeling

Chronic and hemodynamically significant MR can cause LA and LV volume overload, leading to subsequent LA and LV enlargement. The severity of LA and LV remodeling can be assessed by LA to aortic root ratio (LA/Ao), indexed LA diameter (iLA), LV end-diastolic internal dimension to aortic root ratio (LVID/Ao), and normalized LV end-diastolic internal dimension (nLVID).

3.1 LA assessment

Estimation of LA diameter is one of the best predictors of outcome in dogs with MMVD [25, 26]. It also enables to make a decision for the initiation of medication in dogs with preclinical MMVD (ACVIM B1 and B2) and to estimate the risk for development of left-sided CHF [27, 28]. Hemodynamically significant chronic MR generally induces LA volume overload and thus leads to increase in LA volume [29].

In dogs with MMVD, MR causes LA and LV dilation, and thus the assessments of LA and LV chamber dimensions enable clinicians to predict the progression of MMVD and risk of CHF [27, 30–33]. One study evaluated the linear dimensions of the LA, LV, and Ao from the right parasternal long-axis view in dogs with MMVD and found that the mean (standard deviation; SD) for LA/LV, LV/Ao, and LA/Ao in dogs with MMVD were 1.1 (±0.09), 2.7 (±0.5), and 3.0 (±0.5), respectively, compared with 1.0 (±0.05), 2.1 (±0.2), and 2.1 (±0.1), respectively, in healthy control dogs [34]. This study showed good applicability and repeatability of the LA/LV, LV/Ao, and LA/Ao for assessing LV and LA enlargement in dogs with MMVD [34].

Conventional echocardiographic marker assessing LA enlargement is LA/Ao at the aortic root level of LV short-axis plane (**Figure 2A** and **B**). The degree of LA dilation is closely related to the progression of CHF and survival time in both symptomatic and asymptomatic dogs with MMVD [23, 25, 35]. One study enrolled in 558 dogs with MMVD found LA/Ao > 1.7 was the only significant prognostic index among echocardiographic indices [25]. Although the LA/Ao is a major echocardiographic index for determining the degree of LA dilation, the method for measuring the diameter of Ao is not standardized. The first method assessing LA size [36] was as follows: step 1 measures the internal short-axis diameter of the Ao along the commissure between the noncoronary and right coronary aortic valve cusps on the first frame after aortic valve closure and step 2 measures the internal short-axis diameter of the LA in the same frame in a line extending from and parallel to the commissure between the noncoronary and left coronary aortic valve cusps to the distant margin of the left atrium (**Figure 2A**). However, many other studies used a different way of measurement (the second method), i.e. measuring the internal short-axis diameter of the Ao along the commissure between the noncoronary and left coronary aortic valve cusps on the first frame after aortic valve closure (**Figure 2B**). Our study found the Ao diameters measured by the first method were longer than those measured by the second method. Therefore, the LA/Ao measured by the first method was smaller [37]. Because the LA/Ao is a major echocardiographic index for selecting MMVD study groups for drug trials and clinical trials, the standardization of measurement of Ao diameter is required in the future study.

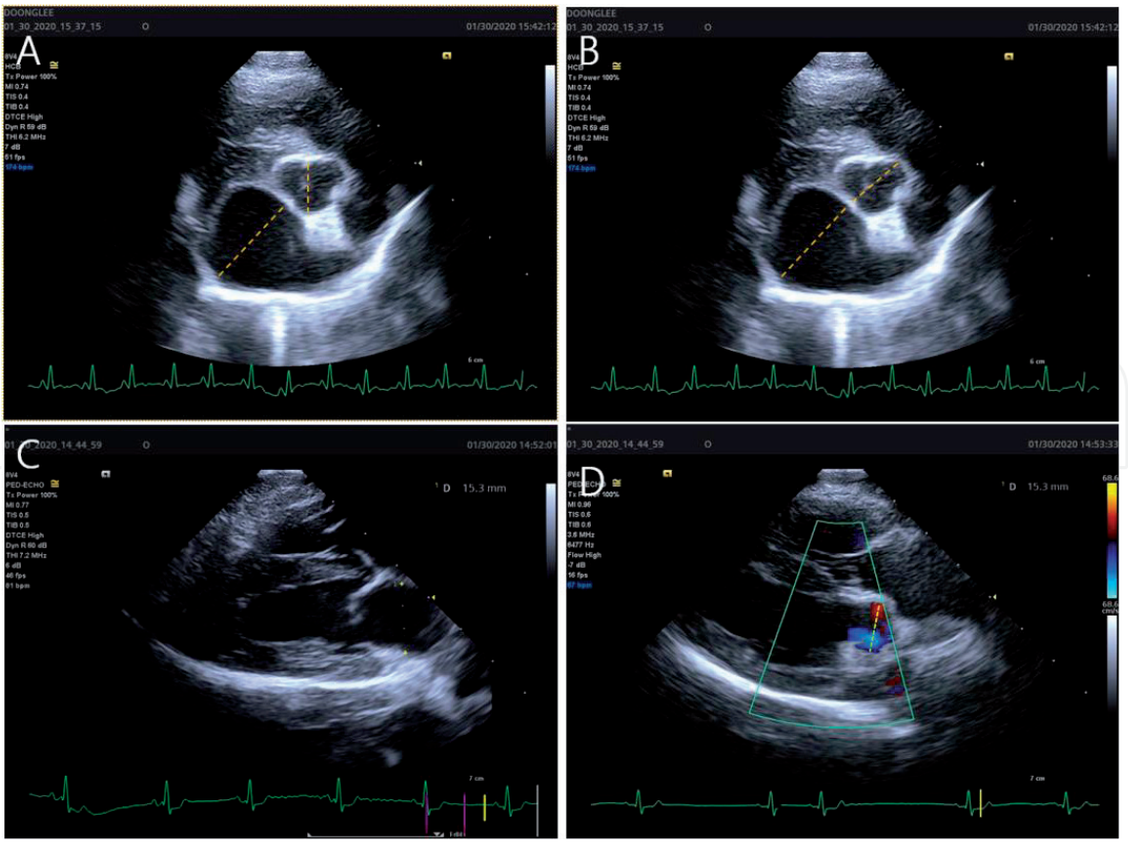


Figure 2.
The method for measurement of left atrial to aortic root ratio (LA/Ao). (A) A LA/Ao obtained from a right parasternal short axis (LA/AoSx) by method 1 (see text). (B) A LA/Ao obtained from a right parasternal short axis (LA/AoSx) by method 2 (see text). (C and D) A LA/Ao obtained from a right parasternal long axis (LA/AoLx). For LA diameter (C), the measurement was made at end-systole 1 to 2 frames before the opening of the mitral valve leaflets. The measurement bisects the atrium extending from the mid-atrial septum in the near field to the bright pericardial echo of the LA lateral wall in the far field and is roughly parallel to the mitral annulus. For Ao diameter (D), the measurement of the aortic valve was made between the opened aortic valve leaflets in an early systolic frame when the Ao diameter is the greatest.

To overcome the problem of LA/Ao at the short axis (LA/AoSx), the LA/Ao was also measured at the long axis (LA/AoLx) [34]. The method measuring LA/AoLx standardized and thus minimized the inconsistency of measurement of LA and Ao (**Figure 2C** and **D**). Several canine studies found cut-offs for LA/AoLx > 2.6 and LA/AoSx > 1.6 indicate hemodynamically relevant MMVD and timing of therapeutic intervention (e.g. enalapril and pimobendan administration) [27, 33].

Indexed LA diameter (iLA) is a good alternative for assessing LA dilation [19]. The iLA is calculated by using the following formula: LA diameter (mm)/(0.795 × body weight [kg])$^{1/3}$. In this study, the iLA diameter had higher sensitivity and specificity for detecting heart disease (healthy control vs. ACVIM B2), despite lower specificity for detecting heart failure (ACVIM B vs. ACVIM C) in dogs with MMVD. Cut-off for iLA > 12.7 indicates the risk of heart failure (ACVIM C) in dogs with MMVD [19].

Because the actual structure of LA is three-dimensional (3D), the LA dilation may occur in all direction (e.g. cranio-caudal, medio-lateral, and ventrodorsal). Therefore, the degree of LA dilation may be overestimated or underestimated, depending on the direction of LA dilation [38, 39]. For this reason, traditional estimation of LA diameter using 2D assessment of LA with linear methods (e.g. LA/AoSx, LA/AoLx, iLA) may not be enough to provide an accurate and consistent measurement. One study measured the LA volume to detect mild LA enlargement using the three-dimensional echocardiography (3D-EC) and found this method

provided a more accurate measurement of LA size than the 2D echocardiography (2D-EC) [40]. Furthermore, the estimation of LA diameter and area by the 2D-EC was shown to have a poor correlation with the 3D-LA volume in humans [41]. However, it is more time-consuming, and substantial off-line analysis is required. Furthermore, the 3D-EC underestimated the LA volumes compared with magnetic resonance imaging (MRI) in human patients [42].

The area-length method (ALM; **Figure 3A**) or monoplane or biplane Simpson's modified method of discs (SMOD; **Figure 3B**) is currently recommended to measure LA area derived from the LA volume [43–46]. In human, the biplane method from four- and two-chamber views is preferred to measure the LA volume [47]. One study evaluated the difference of LA volume measurement by comparing 3D-LA volume measurement to two different 2D-LA volume measurements (using the SMOD and ALM) [48]. In this study, the SMOD and ALM systematically underestimated the LA volume by 7% and overestimated by 24%, respectively, compared with 3D-LA volume (**Figure 3C**). One human study also found the SMOD underestimated the LA volume compared to the 3D-LA volume [49]. Therefore, the 2D-SMOD may be a better method for the estimation of LA volume, if the 3D-EC is not available. One study found the LA volume indices including LA maximal volume (LAVmax) and LA minimal volume (LAVmin) using the ALM was useful to predict survival time when cardiac-related death was only considered [50]. In this study, the LAVmax > 3.53 mL/kg indicated high mortality risk in dogs with MMVD.

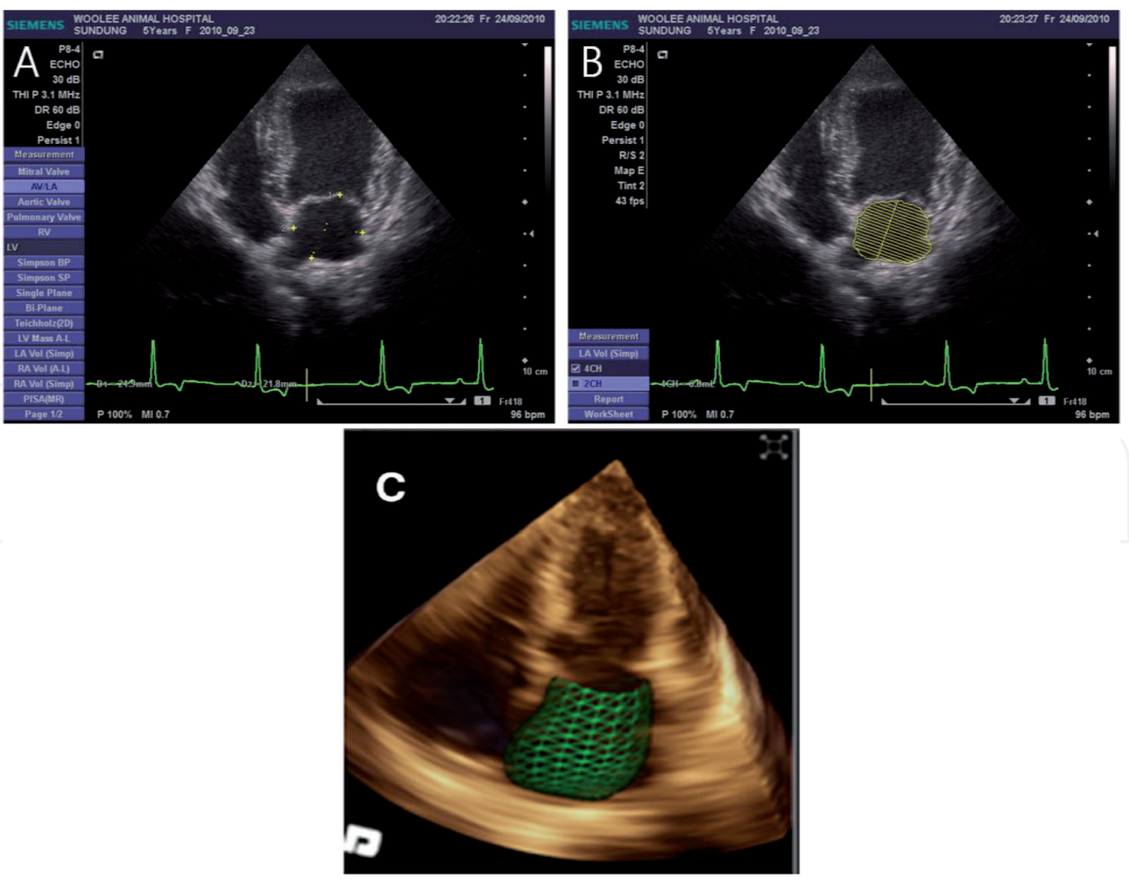
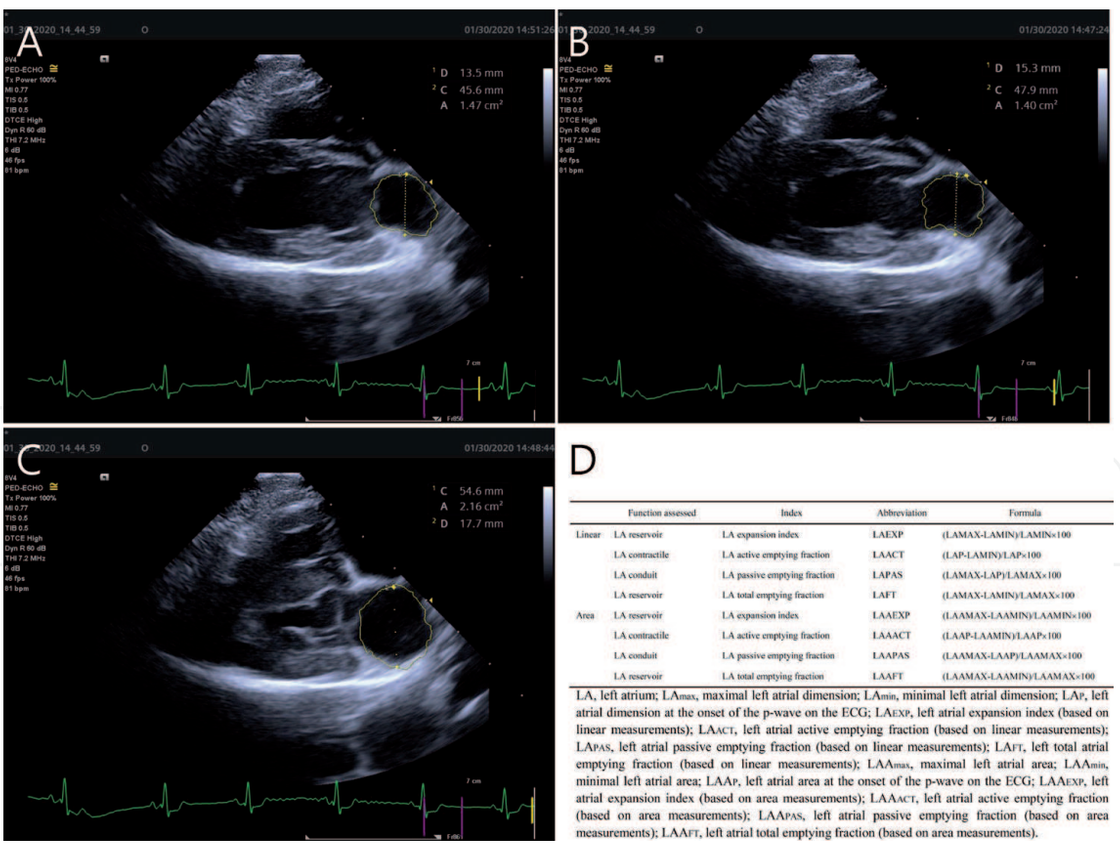


Figure 3.
Left atrial (LA) volume measured for three different methods at a left apical four-chamber view. (A) Area-length method (ALM), (B) Simpson's modified method of discs (SMOD), (C) real-time three-dimensional echocardiography (RT3DE).

Evaluation of the LA function may help to determine the severity of heart failure in dogs with MMVD [40, 44]. The LA function consists of three components: it acts as a reservoir for pulmonary venous (PV) return during ventricular systole (atrial diastole), as a conduit for the passage of stored blood from LA to LV during early ventricular diastole and diastasis, and as an active pump delivering 15–30% of LV filling during late ventricular diastole (atrial systole) [51]. One study established reference intervals for the LA function using 2D linear and area-based estimates and evaluated the diagnostic value to differentiate dogs with asymptomatic (ACVIM B) from symptomatic (ACVIM C) MMVD [52]. This study evaluated four LA functional indices (**Figure 4**): the LA expansion index for LA reservoir, the LA active emptying fraction for LA contractile, the LA passive emptying fraction for LA conduit, and the LA total emptying fraction for LA reservoir. This study demonstrated estimates of LA function except LA passive emptying fraction worsened with the severity of heart failure, although these indices were not sensitive enough to differentiate dogs with asymptomatic from symptomatic MMVD [52].

3.2 LV assessment

Chronic and hemodynamically significant MR can lead to the enlargement of the LV dimension. The degree of LV dilation was strongly correlated with the severity of heart failure in dogs with MMVD [53]. The LV internal dimension can be measured from the 2D or M-mode echocardiography by freezing the image at the



	Function assessed	Index	Abbreviation	Formula
Linear	LA reservoir	LA expansion index	LAEXP	(LAMAX-LAMIN)/LAMIN×100
	LA contractile	LA active emptying fraction	LAACT	(LAP-LAMIN)/LAP×100
	LA conduit	LA passive emptying fraction	LAPAS	(LAMAX-LAP)/LAMAX×100
	LA reservoir	LA total emptying fraction	LAFT	(LAMAX-LAMIN)/LAMAX×100
Area	LA reservoir	LA expansion index	LAAEXP	(LAAMAX-LAAMIN)/LAAMIN×100
	LA contractile	LA active emptying fraction	LAAACT	(LAAP-LAAMIN)/LAAP×100
	LA conduit	LA passive emptying fraction	LAAPAS	(LAAMAX-LAAP)/LAAMAX×100
	LA reservoir	LA total emptying fraction	LAAFT	(LAAMAX-LAAMIN)/LAAMAX×100

LA, left atrium; LA_{max}, maximal left atrial dimension; LA_{min}, minimal left atrial dimension; LA_P, left atrial dimension at the onset of the p-wave on the ECG; LA_{EXP}, left atrial expansion index (based on linear measurements); LA_{ACT}, left atrial active emptying fraction (based on linear measurements); LA_{PAS}, left atrial passive emptying fraction (based on linear measurements); LA_{FT}, left total atrial emptying fraction (based on linear measurements); LAA_{max}, maximal left atrial area; LAA_{min}, minimal left atrial area; LAA_P, left atrial area at the onset of the p-wave on the ECG; LAA_{EXP}, left atrial expansion index (based on area measurements); LAA_{ACT}, left atrial active emptying fraction (based on area measurements); LAA_{PAS}, left atrial passive emptying fraction (based on area measurements); LAA_{FT}, left atrial total emptying fraction (based on area measurements).

Figure 4.
Two-dimensional echocardiographic estimates of left atrial function. (A) the minimal left atrial diameter/area was obtained at the first frame after mitral valve closure (late ventricular diastole), (B) maximal left atrial diameter were obtained at the last frame before opening of the mitral valve (early ventricular diastole), and (C) the mid-left atrial diameter/area was obtained at the onset of the p-wave on the ECG (diastasis). (D) The formula for LA function index.

end-diastole and the end-systole (**Figure 5**). As described above, the LV internal dimension was significantly larger in dogs with MMVD [34]. However, the LV dimensions noticeably vary among breeds of dogs. Therefore, one study evaluated the allometric scaling of M-mode cardiac measurements in normal adult dogs and found a good correlation between M-mode measurements and BW after logarithmic transformation of the data [54]. Therefore, the M-mode-derived LV internal dimension at systole (LVIDs) and diastole (LVIDd) can be transformed into body weight-indexed (normalized) LV internal dimension using the following formulas to obtain a more accurate estimation of LV dilation in dogs with MMVD:

- LV end-diastolic diameter normalized for body weight (LVIDdN) = LVIDd (cm)/weight (kg)$^{0.294}$
- LV end-systolic diameter normalized for body weight (LVIDsN) = LVIDs (cm)/weight (kg)$^{0.315}$

LVIDdN ≥1.7 indicates dogs requiring cardiac medication (>ACVIM B2) [55].

Several studies also found that body surface area (BSA) indexed LV dimensions including end-diastolic index (EDVI) and end-systolic volume index (ESVI) could detect myocardial systolic dysfunction in dogs with MMVD [10, 11, 56]. The EDVI and ESVI can be obtained by the Teichholz formula [57]:

- EDVI = [7 × (LVIDd)^3/(2.4 + LVIDd)]/BSA
- ESVI = [7 × (LVIDs)^3/(2.4 + LVIDs)]/BSA

End-diastolic volume index and end-systolic volume index are obtained by dividing BSA, respectively [57]. Normal values of EDVI and ESVI are <100 and <30 mL/m^2, respectively [57]. One study evaluated the diagnostic accuracy of ESVI using two different methods (i.e. the geometric [GM, based on Teichholz formula] and two planimetric methods [PM, Simpson's derived and area-length methods]) and found that the GM overestimates ESVI in a nonlinear way [11]. However, the

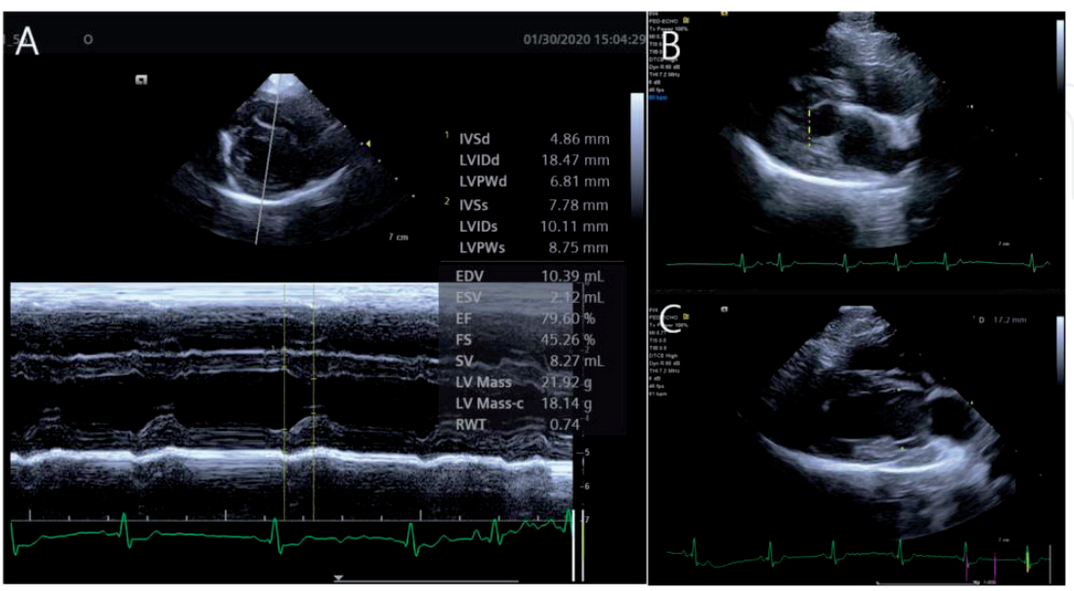


Figure 5.
Measurement of left ventricular internal dimension. (A) M-mode echocardiography obtained from a right parasternal short axis at the papillary muscle level and (B and C) 2D echocardiography obtained from a right parasternal long axis at systole (B) and diastole (C).

	Dog
Diastolic volume	LVd^3 X 7/[2.4 + 3.7 X LVd/(0.795 X $W^{1/3}$)]
Systolic volume	LVs^3 X 7/[2.4 + 5.9 X LVs/(0.795 X $W^{1/3}$)]

LVd, Left ventricle end-diastolic diameter (in cm); LVs, left ventricle end-systolic diameter (in cm); W, weight in kilograms. From "Clinical Echocardiography of the Dog and Cat - E-Book (edited by Madron E, Chetboul V and Bussadori C), St Louis: Elsevier; 2016. pp. 115.

Table 1.
Veterinary Teichholz method formulas for dogs.

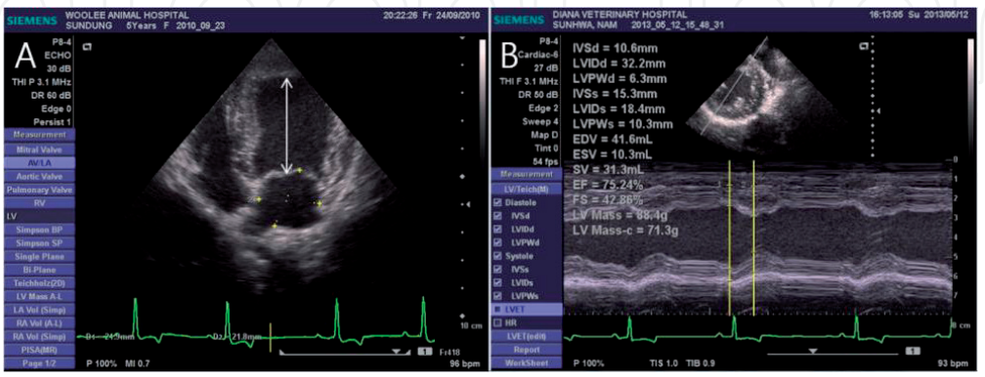


Figure 6.
The left ventricular (LV) sphericity index was calculated by the ratio of LV end-diastolic length (at left apical four-chamber plane; A) to the M-mode LV end-diastolic diameter (B).

ESVI was correlated with the severity of CHF in dogs with MMVD [11]. A recent study also found the EDVI and ESVI obtained from the GM were overestimated and had poor diagnostic values in dogs with MMVD [19]. To overcome this limitation, the veterinary Teichholz formula has been proposed (**Table 1**).

Because sole use of LV dimension often leads to the misestimation of LV dilation, the 2D and M-mode-derived LVIDd/Ao ratio is more appropriate and simpler for evaluating the degree of LV enlargement [14]. However, a recent study found the LVIDd/Ao ratio had high specificity and low sensitivity for detecting asymptomatic dogs from healthy control dogs and symptomatic dogs from asymptomatic dogs with MMVD [19].

Due to the LV dilation, the sphericity of the LV can be increased. One study revealed a significant decrease in the LV sphericity index in dogs with advanced MMVD [11]. The LV sphericity index can be calculated by the ratio of LV end-diastolic length (at left apical two- or four-chamber plane; **Figure 6A**) to the M-mode LV end-diastolic diameter (**Figure 6B**).

4. Assessment of myocardial dysfunction

LV systolic function can be reduced on serial 2D-EC in some dogs with MMVD [10], as noticed in human with advanced CHF [58]. However, LV measurement for systolic function often complicates depending on the LV loading condition, and thus fractional shortening (%FS) and LV ejection fractions (%LVEF) are often increased in dogs with advanced MMVD. In many cases of canine MMVD, when cardiac output is reduced with the progression of MMVD, the LV wall motion becomes more hyperdynamic [10]. Therefore, echocardiographic indices with Doppler for assessing LV functions and filling pressures are often ambiguous by age-related impairment of LV relaxation, LA pressure overload by MR, and impact

on myocardial tissue velocities by LV loading condition. Therefore, echocardiographic indices for LV systolic and diastolic function often lead to the misinterpretation of LV function.

4.1 %FS and %LVEF

LV remodeling caused by chronic and hemodynamically significant MR is characterized by changes in LV geometry in response to chronic volume overload. The common echocardiographic indices for LV systolic myocardial function are %LVEF and %FS. The EF is the volumetric fraction of blood ejected from the LV in each heartbeat (LVEF = [end-diastolic volume − end-systolic volume]/end-diastolic volume × 100). The %FS is defined by the percent change in the dimension from end-diastole to end-systole (FS% = [LVIDd − LVIDs]/LVIDd × 100) [59]. As discussed earlier, %FS and %LVEF are reduced in human with myocardial dysfunction [58]; they are often increased in dogs with advanced MMVD due to hyperdynamic LV contraction from elevated preload and reduced afterload [19, 56]. Therefore, these two indices do not have good diagnostic value for detecting the progression of heart failure in dogs with MMVD [19].

4.2 Spectral Doppler studies

More advanced Doppler and tissue echocardiographic methods are being used for detecting LV dysfunction in dogs with MMVD to overcome problems encountered with the simple measurement of LV geometry.

Continuous-wave Doppler interrogation of MR flow profile can be affected by LA pressure, LV systolic function, and loading condition as well as systemic arterial pressure (SAP) (**Figure 7A**). Although the peak velocity of MR is closely related to MR fraction in the LA but not related to the severity of MMVD in dogs [19], dogs with LV systolic impairment and high LA pressure (as well as markedly reduced SAP) may have decreased peak MR velocity [14]. This may help to differentiate dogs with end-stage CHF from those with ACVIM C and D MMVD. Asymmetric MR flow profiles and a cut-off sign in mid to late systole are often noticed in dogs with the advanced stage of MMVD and are caused by reduction in MR flow due to high LA pressure (**Figure 7B**). The dp/dt is the rate of pressure change over time during isovolumic contraction and closely related to LV systolic function in humans (**Figure 7A**) [60]. However, the dp/dt in dogs with MMVD has limited

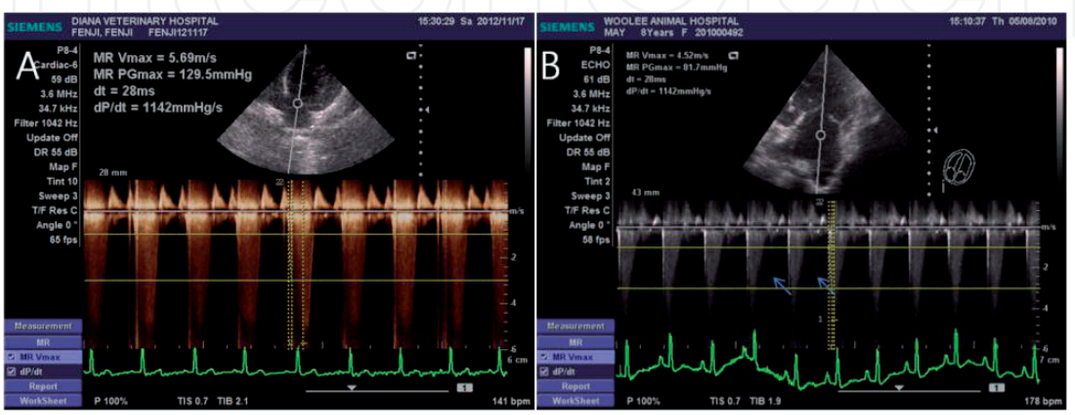


Figure 7.
Continuous-wave (CW) Doppler flow profile obtained from dogs with severe mitral regurgitation (MR). (A) The MR peak velocity and pressure gradient were 5.69 m/s and 129.5 mmHg, respectively, in this dog. (B) Asymmetric MR flow profiles and cut-off signs (arrow) in mid to late systole obtained from the advanced stage of mitral valve disease (see text).

value, because most MMVD dogs may have high peak velocity and asymmetric MR profiles, regardless of the severity of MMVD [18], although some authors proposed its use for detecting LV systolic function [2].

Pulse-wave Doppler interrogation of transmitral flow profile is closely correlated with the stage of MMVD in dogs [14, 18, 19]. The transmitral flow profile consists of an early E-peak (rapid LV filling) and a late diastolic A-peak (atrial contraction) and is closely related to diastolic LV function (LV relaxation/compliance, LV volume overload/pressure overload, and recoil) as well as LV filling pressure (**Figure 8A**) [61, 62]. Although E/A reversal (E/A < 1) is common in the aged canine population, E-peak is higher than A-peak in general canine population (i.e. E/A < 1). One study found 0.87 ± 0.13 m/s (E-peak) and 0.61 ± 0.12 m/s (A-peak) in 100 healthy dogs [63]. A high-velocity E-peak (>1.5 m/s) indicates marked elevation of LA pressure [10] and is correlated with severity of CHF and survival time in dogs with MMVD [18, 19, 23, 25]. Generally, a higher E-peak with a shorter E deceleration time (<80 ms in dogs older than 10–12 years) indicates marked LA pressure overload and non-compliant LV, while an E/A ratio <1 and/or a prolonged E deceleration time indicates impaired relaxation [10]. Because the E-peak velocity is increased with the elevation of LA pressure whereas decreased with impairment of LV relaxation, transmitral flow profile sometimes misleads the severity of LV myocardial dysfunction. However, myocardial and annular velocities are less load-dependent than transmitral flow profile, and thus the E/e (the early longitudinal mitral annular velocity measured by tissue Doppler imaging) ratio is found to better reflect LV filling pressure in dogs with MMVD [61]. A decrease in e-peak at mitral annulus

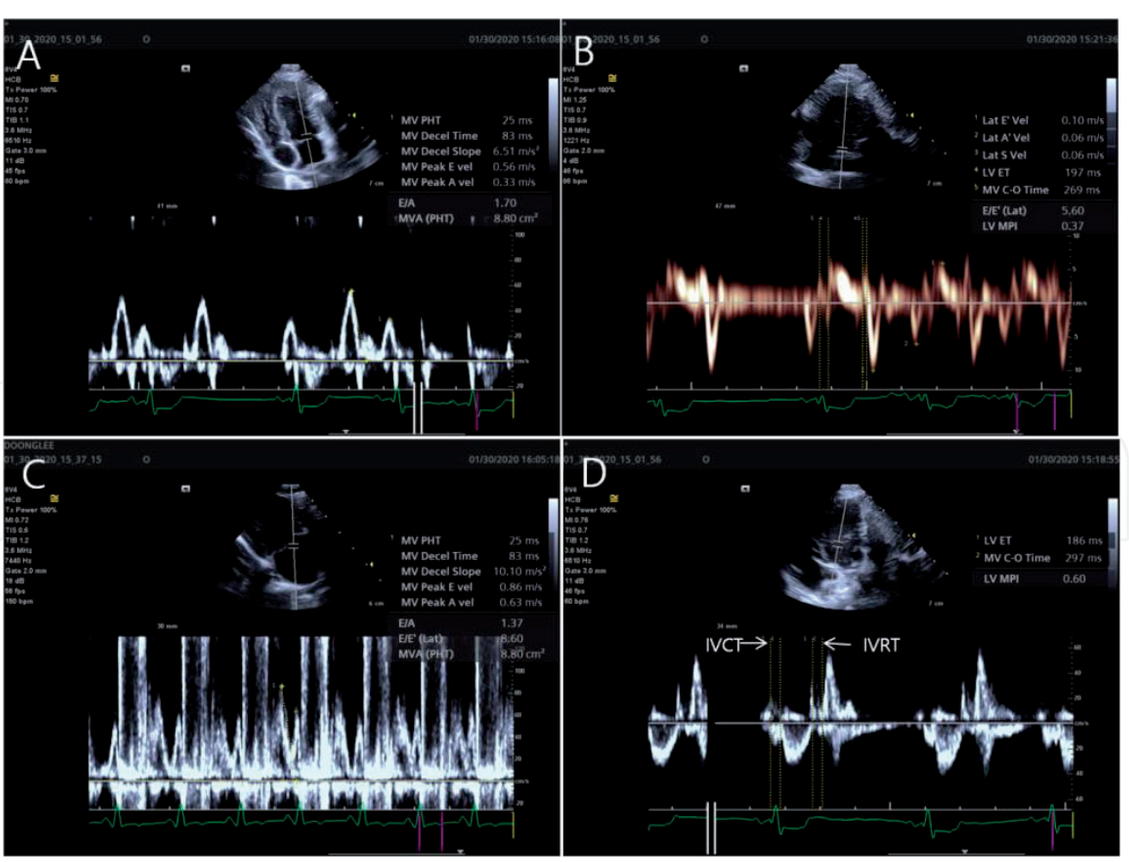


Figure 8.
Transmitral E/e ratio and E/IVRT (the isovolumic relaxation time). (A and B) Transmitral E-peak obtained from a left apical four-chamber plane and tissue Doppler imaging of lateral e-peak obtained from a left apical four-chamber plane. (C and D) Transmitral E-peak obtained from a left apical four-chamber plane. By moving sampling gate towards the midline of the aorta and mitral annulus, aortic and mitral flows were obtained simultaneously. The IVRT was measured from the end of the aortic flow to the beginning of the mitral E-peak.

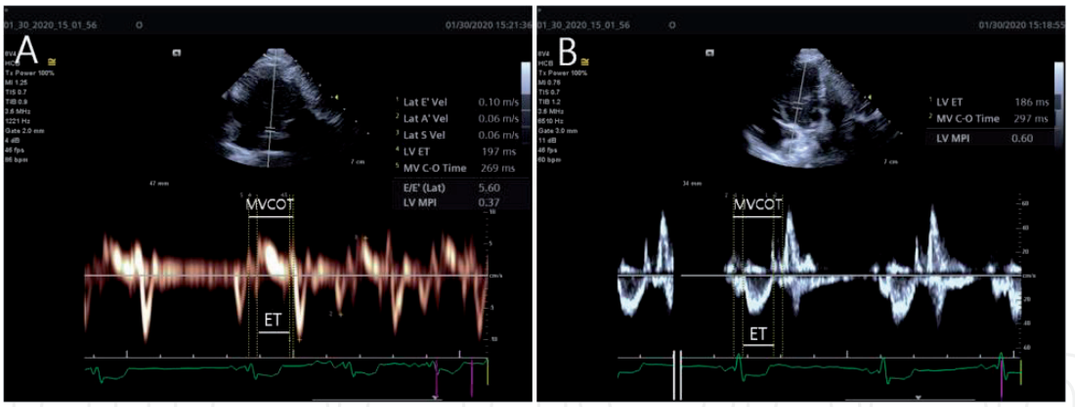


Figure 9.
*Two methods for measuring left ventricular (LV) Tei index. (A) Tissue Doppler imaging at the mitral annulus and (B) Pulse-wave Doppler interrogation at the midline of the aorta and mitral annulus (see **Figure 8D** for the measurement). (See text for more information).*

indicates impaired relaxation. One study revealed an E/e ratio >9 was equivalent to >20 mmHg of LA pressure (95% probability in a canine model of acute MR) (**Figure 8B**) [61]. Furthermore, >12 of E/e along with a high E-peak velocity was able to detect the presence of CHF in this study population [61]. One recent study also demonstrated an E/e cut-off value of 13 identifies CHF with high sensitivity (80%) and high specificity (83%) [64]. Although the e-peak is less affected by LV loading condition, it can be also affected by age and severe LV volume overload, and thus the E/e ratio may have limited value in this situation [14]. Several studies demonstrated E-peak/isovolumic relaxation time (E/IVRT) was correlated with LA pressure and end-diastolic LV pressure in dogs (**Figure 8C** and **D**) [62, 65, 66]. The IVRT may be decreased with the elevation of LV filling pressure. One study suggested the E/IVRT ratio >2.5 and an IVRT <45 ms might indicate the presence of CHF in dogs with advanced MMVD [62]. PW Doppler interrogation of the pulmonary venous flow profile gains popularity to determine LA volume and pressure overload by severe MR in humans [67]. However, it has limited value in dogs with MMVD, due to technical difficulty (e.g. PV usually locates at the far-end of an echocardiographic window) and poor-quality PV profiles (e.g. MR flow often enters into the PV) [14]. The LV Tei index (LV Tei = [IVRT + IVCT + LVET]/LVET, IVCT stands for the isovolumic contraction time) is a valuable index for detecting LV systolic and diastolic dysfunction simultaneously in human with CHF (**Figure 9**) [68]. A human study found shortened LVET/increased LV Tei index in patients with systolic dysfunction and increased mitral valve closure time and Tei index in humans with diastolic dysfunction [69, 70]. One canine study found the LV Tei was closely related to LV dp/dt and was increased with the severity of MMVD [71]. However, in dogs with moderate to severe MR, the IVRT and IVCT are often too short or not detectable [14]. Therefore, the Tei index is rarely used in veterinary fields.

5. Assessment of pulmonary hypertension

Pulmonary venous hypertension (PVH) is a common cause of pulmonary hypertension (PH) in dogs and is prevalent in dogs with MMVD, especially in dogs with the advanced stage of CHF [7, 62, 72]. Gold standard methods detecting PH in dogs are Doppler assessment of peak tricuspid regurgitation (TR) and pulmonic regurgitation (PR) jet velocities [7]. One study demonstrated the Doppler evidence of PH was more evidenced in dogs with more advanced MMVD [7]. Another study also found that dogs having moderate to severe PH had a poorer outcome than in MMVD dogs [72].

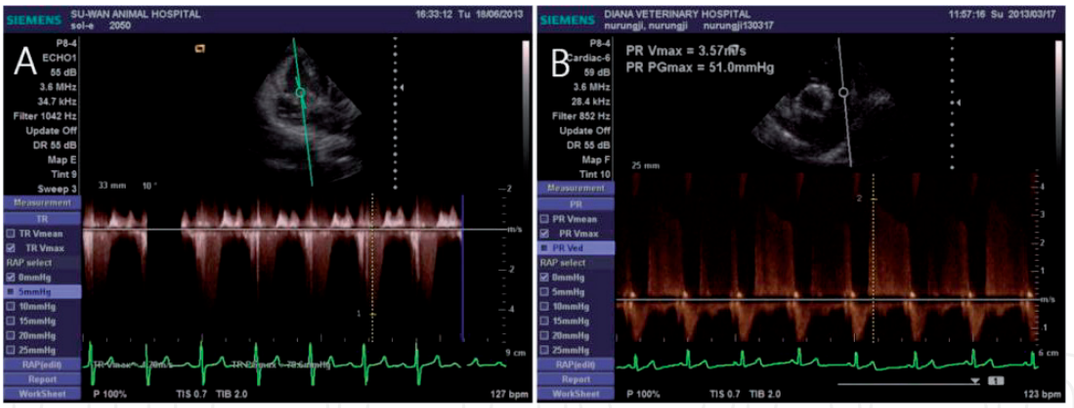


Figure 10.
Echocardiographic evidence of pulmonary hypertension. Continuous-wave Doppler study showing severe tricuspid regurgitation (A) and pulmonic regurgitation (B). (See text for more information).

5.1 Doppler interrogation of TR and PR jets

The peak velocity of TR jet (obtained from either a right parasternal short-axis view or a left parasternal four-chamber view) represents the systolic pulmonary artery pressure (sPAP) if there is no right ventricular outflow tract (RVOT) obstruction [73]. The systolic pulmonary artery pressure can be calculated by applying the modified Bernoulli equation ($\Delta P = 4 \times \text{velocity}^2$) to the peak velocity of TR (**Figure 10A**) or PR jets (**Figure 10B**) and adding the right atrial pressure (RAP): $\Delta P + \pi$ right atrium. The estimated right atrial pressure is 5 mmHg in dogs without any evidence of RA dilation; 10 mmHg in dogs with evidence of RA dilation, but no signs of right-sided heart failure (R-HF); and 15 mmHg in dogs with evidence of RA dilation and clinical signs of R-HF. Then mean pulmonary arterial pressure (mPAP) can be calculated using the following equation: mPAP = 0.61 × sPAP +2. In dogs having the only PR, the mPAP can be calculated using the following equation: PR peak pressure gradient + RAP. A mPAP <25 mmHg is considered normal, while mPAP 25–40 (equivalent to 2.8–3.4 m/s of peak TR velocity), 41–55 (3.4–4.3 m/s), and >55 mmHg (>4.3 m/s) are considered mild, moderate, and severe, respectively [73]. Because the peak velocity is closely correlated with the beam alignment of jet, it often underestimates the severity of PH, if the beam is not parallel to jet [18]. Another study also claimed that the Doppler estimation of SAP often overestimated PH in dogs with MMVD [73]. Since some dogs with PH may have no or insufficient Doppler evidence of PH (e.g. TR or PR jets), other echocardiographic evidence of PH should be pursued in dogs having R-CHF signs or persistent coughing [14]. Despite these limitations, canine studies found the SAP showed good prognostic value for detecting the progression of CHF and the survival time in dogs with MMVD [7, 62, 72].

5.2 2D-EC evidence of PA/RVOT dilation

The 2D-EC evidence of PA/RVOT dilation is the simplest way to detect the existence of PH in dogs with MMVD [35, 74–77]. Since chronic pressure overload and volume overload in RV can cause RV concentric hypertrophy (thickened RV free wall) and eccentric hypertrophy (RV dilation), respectively, simple 2D measurements of RV free wall thickness and dimension may help to identify dogs with PH [74, 78]. Furthermore, LV eccentricity (obtained from right parasternal short-axis view at papillary level; a ratio of longitudinal to the transverse length of LV chamber; **Figure 11C**) is also a simple echocardiographic index for detecting the existence of PH in dogs [78]. Two studies found the LV eccentricity becomes <1, as

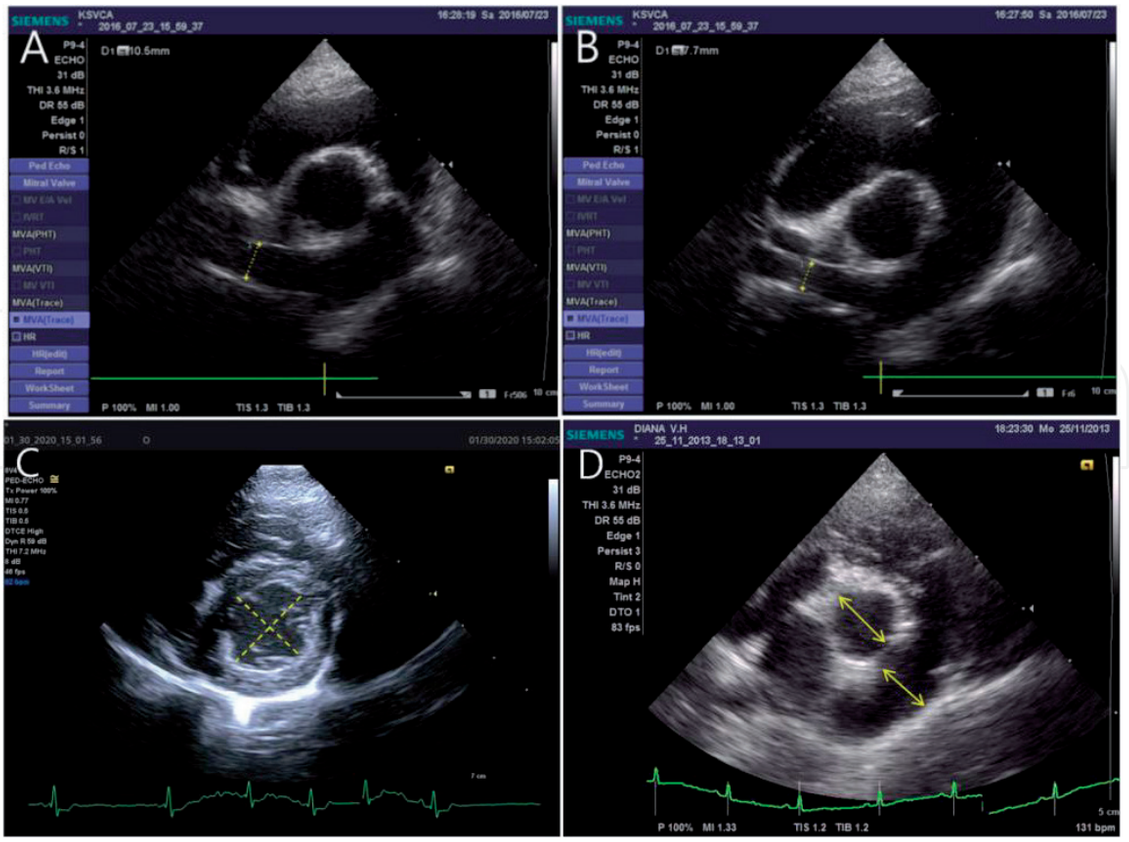


Figure 11.
2D echocardiographic interrogation of pulmonary hypertension. (A and B) right pulmonary artery distensibility index (RPADi) is the difference in diameters of the right pulmonary artery (RPA) at systole (A) and diastole (B) obtained from either 2D or M-mode echocardiography at a right parasternal short axis of PA. (C) Left ventricular (LV) eccentricity obtained from right parasternal short-axis view at papillary level (a ratio of longitudinal to the transverse length of LV chamber). (D) The ratio of main pulmonary artery diameter to aortic root diameter obtained at a right parasternal short axis of PA. (See text for more information).

the RV pressure becomes higher than the LV pressure (as commonly seen in dogs with PH) [74, 79].

In normal dogs, the diameters of the main pulmonary artery (MPA) are roughly identical, and thus MPA/Ao ratio should be close to 1 (**Figure 11D**). Therefore, MPA/Ao ratio > 1 indicates the PA dilation meaning the existence of PH, unless there is RVOT obstruction. Many studies revealed the dilation of MPA in dogs with PH [35, 74–77].

Right pulmonary artery distensibility index (RPADi) is the difference in diameters of the right pulmonary artery (RPA) at systole and diastole obtained from either M-mode right parasternal short-axis (**Figure 11A** and **B**) or long-axis four-chamber view (**Figure 12A**) of PA [77, 80]. One canine study suggested that a RPADi <35 is indicative of PH, while values of 28–35, 23–27, and <23 are indicative of mild (30–55 mmHg), moderate (56–79 mm Hg), and severe PH (>79 mm Hg), respectively [80]. Further study also found that the RPADi was closely correlated with the sPAP [77]. However, the reference range of RPADi was significantly different, depending on the echocardiographic views [77, 80].

RVOT-%FS indicates RV systolic function and can be obtained from M-mode measurement of the RVOT of the right parasternal short-axis view at the level of the aortic root using the following formula: ([RVOT dimensions at end-diastole − RVOT dimensions at end-systole]/RVOT dimensions at end-diastole) × 100 (**Figure 12B**) [81]. One recent canine study found the RVOT-%FS is significantly decreased (<45%) in dogs with PH [82]. However, the RVOT-%FS can be affected by other diseases causing RV systolic dysfunction.

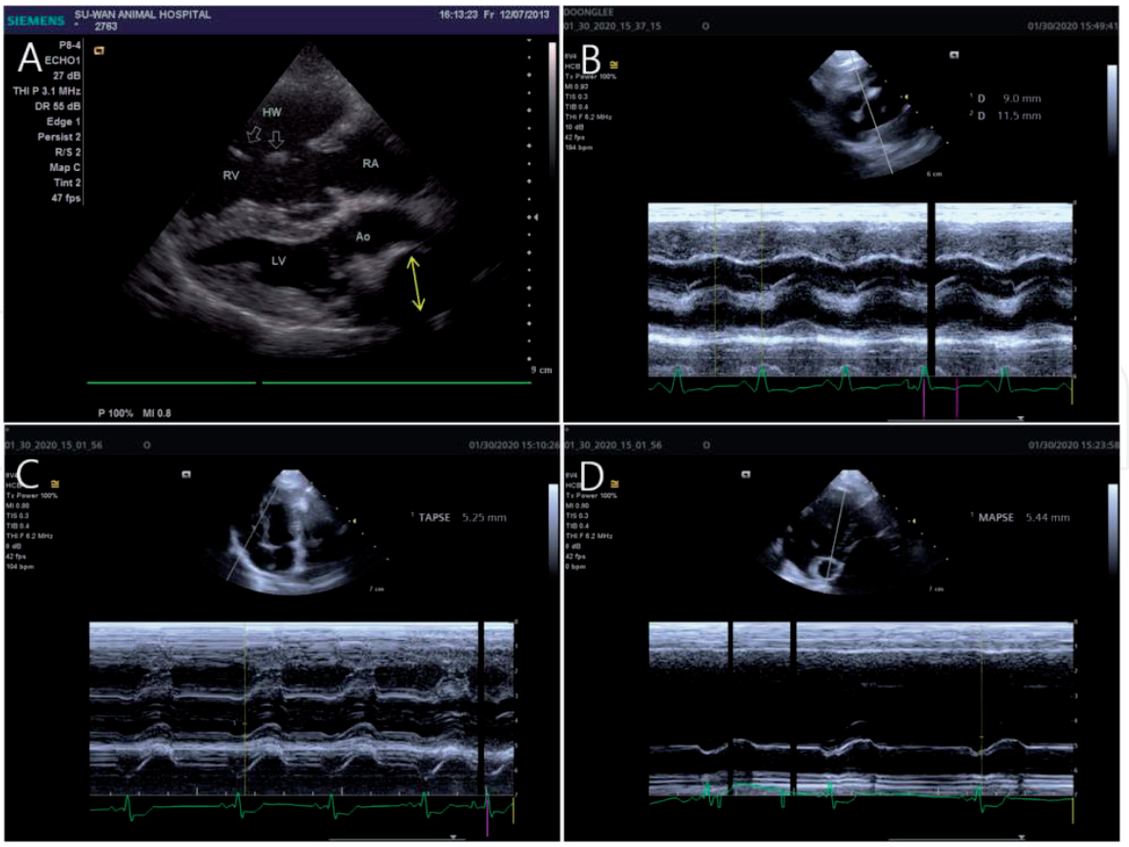


Figure 12.
2D and M-mode echocardiographic interrogation of pulmonary hypertension. (A) Right pulmonary artery distensibility index (RPADi) can be obtained from a right parasternal long axis of four-chamber plane (arrow). (B) Right ventricular outflow tract fractional shortening (RVOT-%FS) obtained from M-mode measurement of the RVOT of the right parasternal short-axis view at the level of the aortic root. Tricuspid (TAPSE; C) and mitral (MAPSE; D) annular plane systolic excursion obtained from a left apical four-chamber plane of M-mode echocardiography. (See text for more information).

Tricuspid annular plane systolic excursion (TAPSE) also reflects RV systolic function, which can be significantly affected by RV pressure overload [83]. Recent canine studies found dogs with PH had lower TAPSE, indicating pressure overload in the RV chamber [75, 84]. The TAPSE can be obtained from M-mode echocardiography that aligned the beam to the lateral tricuspid annulus in the left apical long-axis four-chamber view by calculating the maximal and the minimal excursion of lateral tricuspid annulus motion (**Figure 12C**) as similar to the measurement of mitral annular plane systolic excursion (MAPSE; **Figure 12D**). However, the TAPSE is influenced from the size of dogs; recent studies used body weight-normalized TAPSE (nTAPSE = TAPSE/[BW(kg)]$^{1/3}$) and TAPSE to Ao ratio to overcome the influence of body size [82, 85]. The median (range) of nTAPSEs were 0.60 (0.53–0.66) in ACVIM B1, 0.71 (0.64–0.84) in B2, and 0.73 (0.58–0.80) in C and D MMVD dogs [85]. Other study found the TAPSE/Ao ratio was closely correlated with the size of the LA in dogs with MMVD and PH [82]. The TAPSE/Ao ratio <0.65 was indicative of the presence of PH in dogs with MMVD, although it showed low sensitivity for detecting PH [82].

5.3 Doppler interrogation of PA flow profiles and related variables

Several studies evaluated quantitative echocardiographic variables related to PH in humans and dogs [78, 86–89]. Among those echocardiographic variables, PW Doppler-derived acceleration time to peak PA flow velocity (AT), AT to the ejection time of PA flow ratio (AT/ET) (**Figure 13A**) [86], the right ventricular Tei

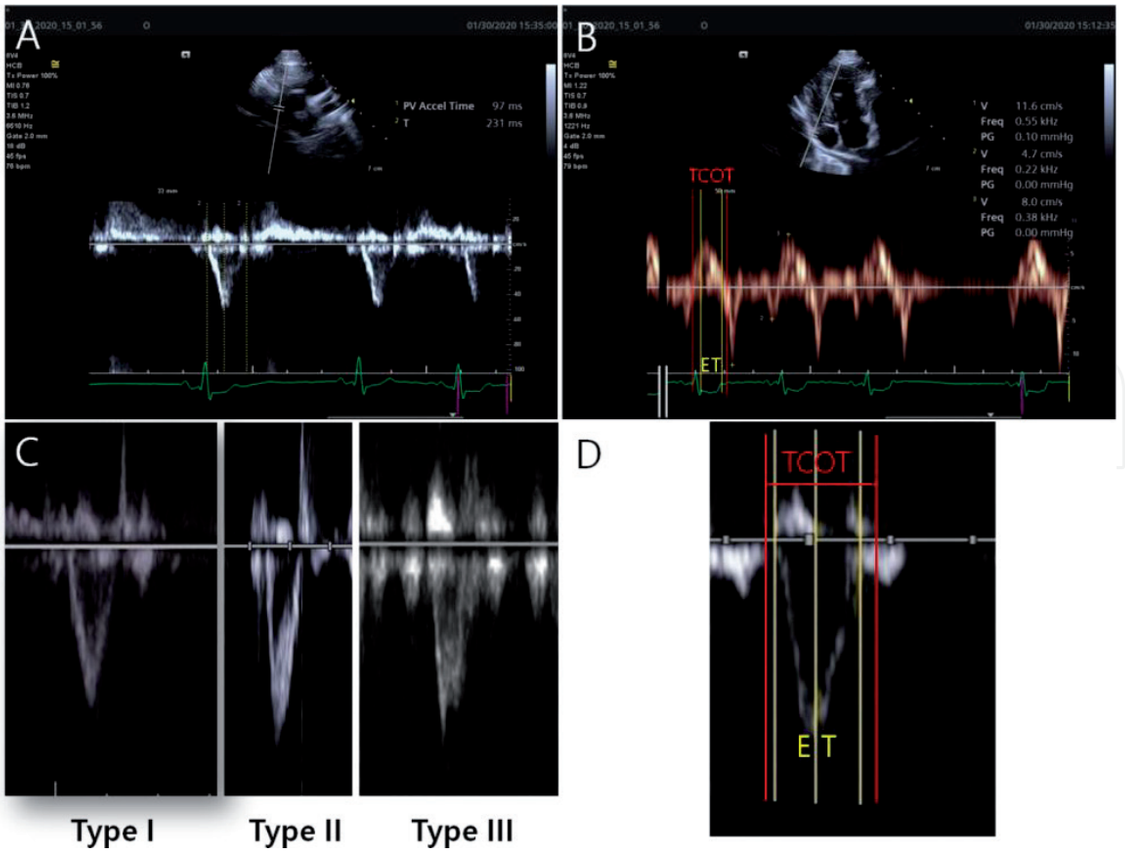


Figure 13.
Pulse-wave and tissue Doppler interrogation of pulmonary hypertension. (A) PW Doppler-derived acceleration time (AT) to peak pulmonary artery (PA) flow velocity (AT), AT to the ejection time (ET) of PA flow ratio (AT/ET). (B) Tissue Doppler-derived right ventricular Tei index (RV Tei), (C) PW Doppler-derived pulmonic outflow profiles, (D) PW Doppler-derived RV Tei index. (See text for more information).

index (RV Tei) (**Figure 13B** and **D**) [89], and Doppler pulmonic outflow profiles (**Figure 13C**) [90] are being used to interrogate PH in dogs. One study found AT, AT/ET ratio, and RV Tei index are strongly correlated with sPAP in dogs without detectable PR [35]. Especially, AT/ET ratios ≤0.25 were predictive of PH, whereas AT/ET ratios >0.42 ruled out PH [86]. However, other study found Doppler estimated mPAP was strongly associated with AT and AT/ET, but weakly associated with RV Tei index [90]. Over 50% of dogs in International Small Animal Cardiac Health Council (ISACHC) II and III had equivocal value of AT/ET indicating PH (0.25–0.42) in this study, suggesting low sensitivity for detecting PH, although most dogs having <0.25 had detectible TR or PR on echocardiography, indicating high specificity for detecting clinically significant PH [90]. This study also found Doppler pulmonic outflow profiles were closely associated with severity of PH in dogs with MMVD, since the Doppler pulmonic outflow profiles (type I/II/III) were 18/0/0 in control, 22/5/1 in ISACHC I, 21/24/2 in ISACHC II, and 17/40/4 in ISACHC III MMVD dogs [90]. The PW Doppler-derived echocardiographic variables of PA flow may have limited value in dogs with hyperdynamic RV condition because Doppler pulmonic outflow profiles can be influenced by RV loading conditions and systolic function [90]. Although RV-TDI may not be a direct indicator of PH, it can be used to evaluate RV systolic and diastolic function in PH patients. It can be obtained from the basal segment of the internal mid-portion of the RV wall in the left parasternal long-axis four-chamber view (**Figure 13D**). One study evaluated the diagnostic value of peak RV myocardial velocities at systole (Stdi), early (Etdi), and late (Atdi) diastole [35]. Also the global TDI index was calculated using the following formula in this study: global TDI index = Stdi × Etdi/Atdi [35].

This study demonstrated the decrement of the global TDI index and Etdi/Atdi in dogs with PH [35]. Furthermore, global TDI index of <11.8 showed sensitivity of 89% and specificity of 90%, while Etdi/Atdi of <1.12 showed sensitivity of 89% and specificity of 93% for detecting PH in the study population [35].

6. Assessment of cardiac chamber deformation/dyssynchrony

Strain and strain rate imaging is an advanced echocardiographic technique for estimating myocardial segmental deformation, respectively [12, 91]. Myocardial strain (i.e., deformation of a myocardial segment over time; % change from its original dimension) and strain rate (the rate of myocardial deformation; S^{-1}) can evaluate more direct intrinsic myocardial function and are less angle-dependent than TDI-based methods [92–94]. Strain and strain rate can be obtained from LV, LA, and RV wall using STE, feature-tracking echocardiography (FTE), or color TDI technology in the longitudinal, radial, and circumferential planes (**Figure 14**) [83]. Speckle tracking can detect the degree of myocardial deformation from the continuous frame-by-frame tracking of speckles (acoustic markers). By tracking these speckles in the myocardium throughout the cardiac cycle, the direction and velocity of myocardial motion can be determined. By comparing the motion of each speckle, the degree of deformation on each segment of the myocardium can be assessed.

Although precise assessment of LV systolic dysfunction is critical for therapeutic intervention and prediction of progression of CHF in dogs with MMVD, assessment of LV function using conventional echocardiography is often complicated

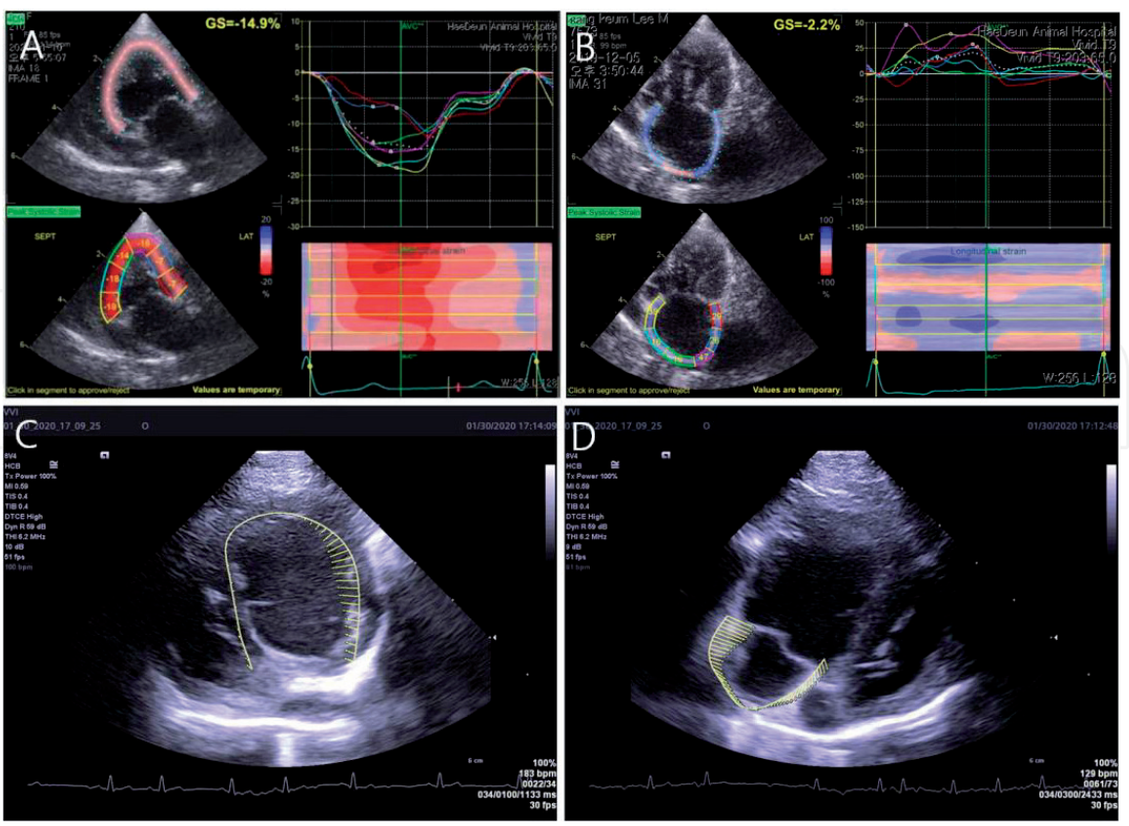


Figure 14.
Representative images of left atrial (LA) and ventricular (LV) strain and strain rate imaging for LA and LV deformation analysis in dogs with mitral regurgitation. (A and B) LV (A) and LA (B) strain profiles obtained from GE analysis software algorithm (EchoPAC). (C and D) LV (C) and LA (D) strain profiles obtained from Siemens vector velocity imaging (VVI). (See text for more information).

with loading conditions [95]. Several studies demonstrated strain and strain rate obtained from the 2D-STE were useful to grade the progression of dogs with MMVD [95–98]. One study claimed the longitudinal strain with the GE analysis software algorithm (EchoPAC) was inconsistent and less repeatable, while radial strain curves from short-axis images were more consistent and more repeatable (**Figure 14A** and **B**) [95]. Since the software algorithm for strain is automated, special attention should be focused on "(1) timing of the ECG to select the cardiac cycle and the onset and duration of analysis; (2) tracing of the endocardial border for automated detection; (3) inspecting the region of interest; (4) following the tissue tracking in real-time and slow-motion; and (5) inspecting the generated curves relative to the R-waves and aortic valve closure (AVC)" as described in Smith et al. [95]. A velocity vector imaging (VVI) is another form of strain analysis, which can display tissue velocity as a vector showing the amplitude and direction of the movement (**Figure 14C** and **D**) [99].

Atrial myocardial deformation profiles estimated by TDI and 2D-STE (e.g. strain and strain rate) have been recently emerged as a good alternative method of exploring LA mechanics in both humans and dogs [100–103]. Although many drawbacks of this approach were noticed (e.g. suboptimal reproducibility, angle dependence, and the confounding effect of noise artifacts), 2D-STE can be a more advanced angle-independent echocardiographic technique for the direct evaluation of LA function than standard grayscale echocardiographic images [100–103]. The specific STE variables subject to the LA function include peak atrial longitudinal average strain (PALS), peak atrial contraction average strain (PACS), and contraction strain index (CSI), which reflect the LA function during its reservoir, booster pump phase, and the contribution of LA active contraction to the LV filling phase (**Figure 14B**) [104]. In humans, LA strain analysis has been useful for grading patients with valvular diseases, atrial fibrillation, or acute coronary disease [105–107]. However, a recent canine study found the STE variables were not significantly different between ACVIM B1 and B2 groups, although those (especially, PALS) were significantly different between ACVIM B2 and C groups [108]. The use of cut-off for PALS <27.9% enables to perfectly differentiate dogs in ACVIM stage B2 from those in ACVIM stage C with a sensitivity of 100% and specificity of 100% [108]. Another study also demonstrated the STE variables including PALS, PACS, and CSI were significantly decreased with the progression of MMVD [103]. A further study from this study group also found the STE variables (PALS <30% and CSI per 1% increase) were predictors of cardiac death in the univariate analysis [109].

Since the RV chamber is crescent-shaped and is wrapped around the LV, precise echocardiographic assessment of RV function is often difficult. The TDI and STE can overcome this limitation as reported in human studies [110, 111]. Recent canine study found the STE on RV was applicable and repeatable in healthy dogs [93]. Furthermore, other study demonstrated the RV longitudinal strain and the dyssynchrony index were significantly different from control dogs [75]. In this study, the global, free wall, and septal RV longitudinal strain in dogs with precapillary PH were significantly lower than those in control, while free wall and septal systolic shortening time strain were significantly slower [75].

7. Conclusion

In this chapter, we described echocardiographic features of MMVD in dogs along with human echocardiographic criteria of MR. Although there are many similarities for diagnosing and grading the severity of MR in both species,

veterinary cardiologists are more focused on the severity of cardiac remodeling and cardiac dysfunction caused by MR, because surgical restoration of defected mitral apparatus is rarely done in dogs. Recent canine studies also found advanced ultrasound technologies, such as strain and strain rate imaging, and two-dimensional speckle tracking echocardiography were also applicable for dogs with MMVD, although more studies are warranted for standardizing the method of assessment in dogs. The authors believe that this chapter would be a valuable reference for veterinary and human cardiologists and researchers for understanding mitral valve disease.

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Conflict of interest

There is no conflict for this publication.

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