Echocardiographic assessment of canine degenerative mitral valve disease

Valérie Chetboul, DVM, PhD a,b,*, Renaud Tissier, DVM, PhD b,c

a Université Paris-Est, Ecole Nationale Vétérinaire d’Alfort, Unité de Cardiologie d’Alfort (UCA), Centre Hospitalier Universitaire Vétérinaire d’Alfort (CHUVA), 7 avenue du général de Gaulle, 94704 Maisons-Alfort cedex, France
b INSERM, U955, Equipe 03, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil cedex, France
c Université Paris-Est, Ecole Nationale Vétérinaire d’Alfort, Unité de Pharmacie-Toxicologie, 7 avenue du général de Gaulle, 94704 Maisons-Alfort cedex, France

Received 6 September 2011; received in revised form 30 October 2011; accepted 1 November 2011

KEYWORDS
Canine; Doppler; Echocardiography; Strain; Tissue Doppler

Abstract  Degenerative mitral valve disease (MVD), the most common acquired heart disease in small-sized dogs, is characterized by valvular degeneration resulting in systolic mitral valve regurgitation (MR). Worsening of MR leads to several combined complications including cardiac remodeling, increased left ventricular filling pressure, pulmonary arterial hypertension, and myocardial dysfunction. Conventional two-dimensional, M-mode, and Doppler examination plays a critical role in the initial and longitudinal assessment of dogs affected by MVD, providing information on mitral valve anatomy, MR severity, left ventricular (LV) size and function, as well as cardiac and vascular pressures. Several standard echocardiographic variables have been shown to be related to clinical outcome. Some of these markers (e.g., left atrium to aorta ratio, regurgitation fraction, pulmonary arterial pressure) may also help in identifying asymptomatic MVD dogs at higher risk of early decompensation, which remains a major issue in practice. However, both afterload and preload are altered during the disease course. This represents a limitation of conventional techniques to accurately assess myocardial function, as most corresponding variables are load-dependent. Recent ultrasound techniques including tissue Doppler imaging, strain and strain rate imaging, and speckle tracking echocardiography, provide new parameters to assess regional and global myocardial performance (e.g., myocardial velocities and gradients, deformation and rate of deformation, and mechanical synchrony). As illustration,
the authors present new data obtained from a population of 91 dogs (74 MVD dogs, 17 age-matched controls) using strain imaging, and showing a significant longitudinal systolic alteration at the latest MVD heart failure stage.

© 2012 Elsevier B.V. All rights reserved.

Introduction

Degenerative mitral valve disease (MVD) is the most common acquired canine heart disease. Its prevalence can attain 14%–40% in small-sized dogs depending on the breed, and even reaches higher values in geriatric canine populations. Large breed dogs such as German Shepherds can also be affected by the disease. Whichever the canine breed considered, MVD 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), the severity of which is a major determinant of the natural disease progression. Although most dogs with MVD remain asymptomatic for years and even for life, severe complications can occur concomitantly with MR worsening, including left- and then right-sided congestive heart failure secondary to pulmonary arterial hypertension (PAH). This ultimately leads to death or euthanasia due to unresponsive symptoms.

Because of the potential deleterious consequences and high prevalence of MVD, its accurate diagnosis and the monitoring of its progression over time are critical clinical concerns for predicting the risk of decompensation, guiding prognosis and adapting medical prescription.

The standard transthoracic echocardiographic examination is currently considered as the non-invasive diagnostic method of choice for early detection of the mitral valve lesions, evaluation of MR severity, and lastly, for assessing its impact on cardiac remodeling, myocardial function, left ventricular (LV) filling pressures as well as pulmonary arterial pressure. However, owing to volume overload and complex hemodynamic changes associated with disease progression, the detection of myocardial dysfunction in the setting of chronic MR still remains challenging. Nevertheless, more recent advances in ultrasound technology, together with the introduction of other imaging modalities such as tissue Doppler imaging (TDI), strain and strain rate imaging, and two-dimensional (2D) speckle tracking echocardiography (STE), currently offer new opportunities for assessing and monitoring global and regional myocardial function over time.

The present article provides a review of the conventional echocardiographic alterations associated with canine MVD, including a critical approach to the assessment of LV contractile performance, followed by an outline of the more recent ultrasound techniques and their impact on the understanding of MVD-associated myocardial dysfunction.

Identification of mitral valve lesions

Macroscopically mitral valve lesions associated with MVD are firstly characterized by small, smooth nodules on the leaflet tips (Fig. 1) and thickened chordae tendineae (CT), which may be identified by 2D and M-mode echocardiography (Fig. 2). These nodular deformations are usually greater for the anterior leaflet (Fig. 2A and C) and become thicker and more irregular during disease progression. Abnormal systolic flattening of one or both mitral valve leaflets and then mitral valve
Figure 1  Three-dimensional transthoracic echocardiogram obtained from a dog with mild mitral valve disease (view from the apex) showing the nodular deformation of the 2 mitral valve leaflets (arrows). LA: left atrium. LV: left ventricle. LVOT: left ventricular outflow tract.

Figure 2  (2A–2C): Echocardiograms obtained from 3 dogs with mitral valve disease (2A and 2B, two-dimensional right parasternal 5- and 4-chamber views, respectively; 2C, M-mode echocardiogram recorded at the level of the mitral valve). Mitral valve lesions are characterized by the presence of nodules at the leaflet tips (arrows, 2A) and thick chordae tendineae (double arrow, 2B). The nodular deformation is greater for the anterior leaflet (2A). The M-mode image (2C) also shows an irregular thickened anterior mitral valve leaflet (arrow) with a short mitral-interventricular septum distance related to a hyperkinetic state. Ao: aorta. IVS: interventricular septum. LA: left atrium. LV: left ventricle. LVFW: left ventricular free wall.
prolapse, which is characterized by one or both leaflets buckling back into the left atrium (LA) during systole (Fig. I — Data available in Supplemental Data on-line), are also common echocardiographic findings. In one recent study involving 537 dogs with MVD and mitral valve prolapse, a significant correlation was found between the severity of mitral valve prolapse and MR severity as well as the International Small Animal Cardiac Health Council (ISACHC) class.31 Prolapse of the anterior leaflet was present in 48% of the recruited animals, that of the posterior leaflet in only 7%, and bi-leaflet prolapse was detected in 45%. Such a distribution is different from that typically found in humans, where the posterior leaflet is more commonly involved whereas sole involvement of the anterior leaflet is rare.32

Chordae tendineae are major components of the atrioventricular valve apparatus, which determine the position of and tension on the leaflets at end-systole, thus contributing to proper systolic closure of the mitral valve.24 Chordae tendineae rupture (CTR) therefore represents a severe MVD-associated lesion, usually responsible for marked MR. It can be accurately diagnosed using 2D rather than M-mode echocardiography (Fig. II — Data available in Supplemental Data on-line).33,34 Rupture of primary CT is seen in several 2D imaging planes, whereas that of secondary CT is usually identified only in a single view. In one study involving 706 dogs with MVD, CTR was diagnosed in 16% of cases and CTR prevalence was shown to increase with heart failure class.34 In the great majority of dogs (96.5%), the ruptured CT had been attached to the anterior mitral valve leaflet (Fig. II — Data available in Supplemental Data on-line). As expected, all dogs with CTR had moderate (7%) to severe MR (93%), and the prevalence of PAH was relatively high (35%) although most recruited dogs (87%) were under medical treatment.34 Interestingly, 25% of the dogs with CTR were asymptomatic at the time of diagnosis and belonged to either classes 1a (7%) or 1b (18%) of the ISACHC classification (see example in Fig. III — Data available in Supplemental Data on-line). All these were referred for a cardiovascular check-up, because of a left apical systolic heart murmur detected on cardiac auscultation by the referring veterinary practitioner. Similarly, in humans, CTR may be an incidental echo finding (in up to 70% of cases according to studies), and the detection of CTR in asymptomatic patients with MVD is currently an indication of early surgical repair in order to improve long-term survival.35—38 Although, in the canine study, the asymptomatic dogs with CTR represented only 2% of dogs with MVD class 1a and 21% of dogs with MVD class 1b (out of a total of 412 and 96 animals, respectively),34 these data illustrate the potential interest of performing echocardiographic examinations on asymptomatic MVD dogs, in order to help identify those with the most severe lesions that are at a higher risk of decompensation.

Assessment of MR severity

Evaluation of MR severity is of critical importance in dogs with MVD, as MR directly reflects the primary hemodynamic consequence of incomplete apposition of the mitral valve leaflets during systole.

Semi-quantification of MR

One of the methods commonly used to assess MR severity in dogs with MVD consists of calculating the maximal ratio of the regurgitant jet area signal to LA area (ARJ/LAA ratio) using color-flow Doppler mode (Fig. 3).9,10,21 On the basis of this Doppler method, MR is usually considered as mild if the ARJ/LAA ratio is <20—30% (Fig. 3A), moderate if it is ≥20—30% but <70%, or severe if it is >70% (Fig. 3B).9,10,21,39 The major advantage of this color Doppler mapping method is the rapidity and ease of data acquisition,39 and its good repeatability and reproducibility in the awake dog for a trained observer.10 However, this technique only allows a semi-quantification of MR, as the ARJ/LAA ratio compares 2 areas without any assessment of the regurgitant volume. Moreover, the ARJ/LAA ratio may be influenced by several factors including systemic arterial blood pressure, LA pressure, spatial orientation of the jet (eccentric wall-impinging jets can appear smaller than centrally-directed jets of similar hemodynamic severity), pulse repetition frequency and gain settings.39 Another limitation of the ARJ/LAA ratio is that the maximum of 100% is attained in a relatively large percentage of dogs in each heart failure class, which precludes an accurate discrimination between these dogs with “significant” MR.10

The vena contracta is the narrowest portion of the MR jet that occurs at or just downstream from the regurgitant orifice.39 The width of the vena contracta seen by color-flow imaging is a surrogate for the regurgitant orifice size and represents another approach to estimate MR severity.39 However, this method is prone to errors.
Quantification of MR

The PISA (Proximal Isovelocity Surface Area) method, also called the flow convergence method, is another Doppler technique routinely used in human medicine to quantify (rather than "semi-quantify") mitral valve regurgitation (see details in Fig. IV – Data available in Supplemental Data online). Although the PISA method is more time-consuming than color mapping and although many precautions need to be taken to ensure optimal acquisition of the flow convergence images, this technique has been shown to be repeatable and reproducible in the awake-dog for a trained observer. Its main advantage is the more reliable “discrimination” of MR severity compared to the color Doppler mapping method, providing measurement of the flow rate through the regurgitant orifice, calculation of the regurgitant volume, and assessment of the regurgitation fraction (RF, i.e., percentage of stroke volume ejected into the LA during systole). Mitral insufficiency is usually considered as moderate and severe, for RF values higher than 30–50% and 75%, respectively. In several studies performed on dogs with MVD, RF was significantly correlated with clinical parameters (ISACHC class, heart murmur grade), and a significant correlation was demonstrated between RF and several indirect echo-Doppler markers of MVD severity including the LA size as assessed by the LA/aorta ratio (LA/Ao) and systolic pulmonary arterial pressure. A significant correlation has also been shown between N-terminal pro-B-type natriuretic peptide plasma concentrations (NT-proBNP) and RF both in asymptomatic and symptomatic dogs with MVD.

Interestingly, the ARJ/LAA ratio assessed by color Doppler mapping has also been shown to be significantly correlated with RF. The former index may therefore be used to assess MR severity and may also be useful for longitudinal follow-up of canine MVD despite its previously explained limitations. It may also sometimes compensate for several PISA method limitations: the PISA method is more time-consuming and is more accurate for regurgitations with a circular orifice rather than non-circular orifice. Moreover, it may sometimes be difficult to judge the precise location of the orifice and the flow convergence shape. In addition, the PISA method only applies to holosystolic MR. Lastly, the presence of multiple regurgitant jets, which can occur in dogs with MVD, also precludes use of the PISA method.
Indirect assessment of MR severity

Extensive left heart dilation, high LV filling or pulmonary arterial pressures, and echocardiographic signs of congestive heart failure (e.g., pleural and pericardial effusion, and ascites) in dogs with MVD (see below) are all indirect signs of severe MR. Nevertheless, asymptomatic dogs with or even without left heart enlargement (Fig. III — Data available in Supplemental Data on-line) may also show moderate to severe MR, thus indicating that an assessment of MR severity is relevant at this stage. In one study devoted to MR quantification in canine MVD using the PISA method, 10 dogs without clinical signs exhibited a wide range of RF, and approximately one-third of them showed moderate to severe RF. The dispersion of RF values at the asymptomatic stage is also well-known in human patients with MR, and the PISA method is now systematically recommended at this stage for the quantitative grading of mitral incompetence and identification of high-risk patients that might benefit from early medical or surgical treatment. 38,43 Similarly, in one study performed on 72 dogs with asymptomatic MVD, a wide range of RF was found (4—69%), and NT-proBNP in dogs from ISACHC class 1a with mild RF (i.e., RF <30%) was not significantly different from that of healthy control dogs. Conversely, dogs from ISACHC class 1a with moderate to severe MR (i.e., RF >30%) had significantly higher NT-proBNP values than healthy dogs and dogs from ISACHC class 1a with mild RF. Moreover, RF was also higher in dogs that underwent decompensation (cardiac death or development of congestive heart failure) one year after the initial MVD diagnosis. These results suggest that MR severity assessed by RF is one of the major determinants of MVD severity and reflects the latter well, even at early stages of the disease. Serial echo-Doppler examinations for the identification of progressive MR worsening could therefore be recommended to help predict the risk of decompensation in dogs with asymptomatic MVD.

Left heart remodeling, myocardial alteration, and hemodynamic changes

Left atrial overload

Chronic and hemodynamically significant MR results in volume overload, which is first characterized by LA enlargement as assessed by the LA/Ao ratio (Fig. 4). 44,45 An abnormal curved form of the interatrial septum, increased diameter of the pulmonary veins and the presence of atrial arrhythmias are other indirect signs of elevated LA pressure (Fig. V — Data available in Supplemental Data on-line). The high prognostic value of the

Figure 4  Two-dimensional echocardiograms obtained from 2 dogs with mitral valve disease of different severities (right parasternal transaortic views at the level of the aortic valve at end-diastole as described and validated44). 4A: In this ISACHC class 1a dog, the left atrial diameter is still normal with a left atrium/aorta ratio (≈1) within the reference ranges ([0.52—1.13]). 45 4B: Conversely, in this ISACHC class 3 dog, the left atrial diameter is markedly dilated with a left atrium/aorta ratio of 2.86. Ao: aorta. Aur: left auricle. LA: left atrium. RVOT: right ventricular outflow tract.
degree of LA dilation has been demonstrated in both symptomatic and asymptomatic dogs with MVD. In one study involving a large population of dogs with MVD (n = 558), LA/Ao > 1.7 was the only variable significantly associated with survival time when cardiac-related death was considered.

Left atrial rupture related to endocardial splitting of its caudal wall is an infrequent complication of canine MVD, which is characterized by the presence of pericardial effusion with a laminated blood clot in the pericardial space (Fig. 5).

The etiology of spontaneous LA endocardial splitting includes increased LA pressure and mechanical trauma to the atrial endocardium due to severe MR.

Acquired atrial septal defect secondary to atrial septal rupture is another uncommon complication of severe canine MVD (Fig. VI — Data available in Supplemental Data on-line). Such lesions have rarely been described using echocardiography. Atrial septal ruptures usually occur in a thin area of the atrial septum, i.e., close to the fossa ovalis. The degree of shunting depends mainly on the atrial septal defect size and the transatrial pressure gradient. Atrial septal rupture provides a path of lower resistance for the dilated LA, which may be a hemodynamic advantage. However, in the case of considerable left-to-right shunting it may also contribute to right-sided volume overload as well as elevated systemic venous pressure and right-sided congestive heart failure.

Left ventricular remodeling

As MR worsens over time, the volume overload created by MR results in an increase in end-diastolic LV dimensions. This eccentric LV hypertrophy, reflecting a marked increased preload, may in turn worsen MR, by annular dilation and papillary muscle malalignment.

Diastolic LV volumes and diameters can be assessed by M-mode and 2D echocardiography (Figs. VII and VIII — Data available in Supplemental Data on-line; Fig. 6). A recent study, examining the changes in LA and LV dimensions before and at onset of congestive heart failure in Cavalier King Charles Spaniels, showed that the left heart chambers rapidly increased in size only during the last year before the onset of congestive heart failure, thus suggesting that the rate of increase in heart dimensions may be a useful indicator of impending decompensation.

The progression of MVD is also associated with an increased sphericity of the LV: a study performed on 77 dogs with MVD demonstrated a significant decrease in the LV sphericity index (defined as the ratio of LV end-diastolic length to

Figure 5 Left atrial rupture in a Yorkshire Terrier suffering from severe mitral valve disease and referred for recurrent syncope (right parasternal 4-chamber view). Note the irregular and thickened mitral valve leaflet (ml), the presence of pericardial effusion (PE) and the clot appearing like laminar echoes within the pericardial space (arrow). LA: left atrium. LV: left ventricle. RA: right atrium. RV: right ventricle.

Figure 6 Left ventricular M-mode echocardiogram showing myocardial dysfunction in a Cavalier King Charles Spaniel with end-stage mitral valve disease (regurgitation fraction of 79% and high systolic pulmonary arterial pressure of estimated 84 mmHg). Although the left ventricular free wall (LVFW) is hypokinetic, the fractional shortening is still "normal-high" (44%, reference ranges [30-49%]) owing to the great amplitude of the interventricular septal (IVS) systolic motion and the increased left ventricular end-diastolic diameter. Sweep speed is 100 mm/s. LV: left ventricle. RV: right ventricle.
the M-mode LV end-diastolic diameter) with ISACHC heart failure class.23

Systolic myocardial dysfunction

Another potential MVD complication is LV systolic dysfunction (Fig. 6).22,23,51,52 However, the detection of MR-associated systolic dysfunction remains challenging in both humans and dogs.22–28 In humans, assessment of systolic dysfunction associated with MR may rely on a comparison of pre- and post-operative values of echocardiographic variables in patients undergoing mitral valve surgery.24–28,38 Unfortunately, such studies are currently difficult to undertake in veterinary medicine, as surgical repair or replacement of the native mitral valve are very rare treatment options for canine MVD.

Assessment of the ejection fraction (EF%) and the fractional shortening (FS%)

Ejection fraction (%) and FS% are the 2 indices most commonly used to assess systolic myocardial function in the dog by conventional echocardiography.22 As described in Fig. VIII, EF% represents the percent of blood volume ejected from the LV during systole. It is therefore defined by the percent of change in LV volumes between the diastolic and systolic phases (EF% = (EDV – ESV)/EDV *100, where EDV and ESV are the LV systolic and diastolic volumes), and a low EF% value is consistent with decreased systolic function.21–23 As shown in Fig. VII, FS% (which corresponds to a 1-dimensional assessment of myocardial systolic function) is defined by the percent change in radial LV diameters between the diastolic and systolic phases (FS% = (LVD – LVS)/LVD *100/LVD, where LVD and LVS are the LV systolic and diastolic diameters, usually assessed by M-mode echocardiography), and again a low FS% value is consistent with decreased contractility.21,22 In a prospective study performed by our group in 101 small-breed dogs (body weight <15 kg), EF% values assessed in normal dogs, using the monoplane Simpson’s derived method of discs (see Fig. VIII for explanation), were 67 ± 6% [55–75%], and the normal values for FS% were 38.8 ± 4.8% [30–49%].23

Limitation of EF% and FS% in the canine MVD setting

One important limitation of both FS% and EF% is that these indices depend on several factors other than intrinsic myocardial contractility, such as preload and afterload. Evolution of canine MVD is characterized by an increased preload due to MR (see above). In addition, mitral valve lesions create a new pathologic pathway of low resistance for ejection of blood from the LV.24 This “easy” retrograde blood ejection into the LA begins early, before aortic valve opening, as soon as the LV pressure begins to rise in early systole (without any isovolumic contraction period), thus reducing the peak systolic LV wall stress (i.e., afterload).22,24 Therefore, canine MVD progression is mainly characterized by a LV hyperdynamic state with elevated FS% and EF% due to combined volume overload (i.e., LV diastolic dilation), decreased afterload and increased sympathetic tone (Fig. VII — Data available in Supplemental Data on-line). Ejection fraction and FS% are thus rarely decreased, even at advanced MVD stages.21–23 In a study performed on 77 dogs with MVD, a significant increase in FS% and EF% (assessed by 3 different methods) was found from ISACHC class 1 to ISACHC class 3. These 2 indices were also significantly positively correlated with RF in heart failure dogs (ISACHC classes 2 and 3).23 Such elevated values of FS% and EF% are usually associated with exaggerated motions of the interventricular septum and the LV free wall (Fig. VII). Unlike normal dogs, the interventricular septum may exhibit a greater systolic excursion than the LV free wall, probably reflecting changes in LV geometry with deviation of the interventricular septum to the right, associated or not with regional dysfunction of the LV free wall (Fig. 6).21,22

The load dependency of EF% and FS% explains why, in the case of MVD, impaired myocardial function may be associated with normal values of these indices. Therefore, most authors agree that normal values for FS% or EF% in dogs with severe MR suggest systolic myocardial failure.21,22 Although rarely present, hypokinetic myocardial walls may also help in identifying severely decreased contractile performance (Fig. 6). Lastly, progressive (instead of sudden) systolic closure of the aortic valve may be observed using M-mode views at the level of the aortic valve, reflecting a severe decrease in cardiac output due to high RF and/or myocardial systolic dysfunction. Therefore, and to summarize, because of MVD-associated load changes, and except for severe myocardial alterations, the identification of MR-associated myocardial failure remains difficult to evidence using traditional indices.
End-systolic LV dimensions

End-systolic LV dimensions, including end-systolic diameter, end-systolic volume, and end-systolic volume indexed to body surface area (ESVI), are other conventional echocardiographic variables, which may be used to identify systolic myocardial dysfunction in dogs with MVD. Increased end-systolic dimensions, despite enhanced systolic LV ejection into the low-pressure LA chamber, suggest impaired systolic function. The ESVI index has been shown to be a relatively load-independent predictor of post-operative systolic dysfunction in humans with MR and a relatively independent variable of experimental increased preload in the dog. Three ultrasound methods may be used to evaluate ESVI: the Teichholz method, also called the geometric method, based on M-mode linear measurement of the LV systolic diameter, and 2 planimetric methods including the monoplane Simpson’s derived method of discs and the length-area method (see Fig. VIII for explanation). Unlike planimetric methods, the Teichholz method does not involve direct measurement of longitudinal LV dimension. Our group has demonstrated that MVD progression is associated with changes in LV shape (increased sphericity), which was recently confirmed by 3D echocardiography. Because the Teichholz formula does not take into account this progressive change in LV shape during the time course of the disease, the geometric method is inaccurate for assessing LV volumes in dogs with MVD. This inadequacy of the Teichholz method, as compared to the 2 other “anatomy-based” methods, was confirmed by the Bland–Altman results, which showed that the Teichholz method overestimates ESVI in a non-linear way. This bias is of major practical importance because it means that the Teichholz method leads to an overestimation of LV size (and therefore an overdiagnosis of systolic dysfunction) in canine MVD that becomes more marked with disease progression. Similar results were obtained by Tidholm et al. who showed that the Teichholz method overestimates LV volumes in dogs by a factor of approximately 2 in comparison with real-time 3-dimensional echocardiography, whereas a good agreement exists between the latter and the Simpson’s method. The Teichholz method should therefore not be recommended to assess ESVI in dogs with MVD. When planimetric methods are used, ESVI has been found to be significantly increased in dogs with advanced MVD, with a negative prognostic value on survival at 5 months. As breed reference intervals are lacking for ESVI assessed by planimetric methods and as the repeatability and reproducibility of these variables have been shown to be good for a trained observer (coefficients of variation <11%), repeated measurements of this variable over time (along with EF% value) may be recommended to help identify ongoing myocardial dysfunction in a given MVD dog.

Other variables

The LV Tei index, assessed by pulsed-wave Doppler examination of transmitral and aortic flows, is defined as the sum of the isovolumic contraction and relaxation times divided by the ejection time. Although rarely used in practice, the LV Tei index (or index of myocardial performance) has been shown to be significantly correlated with the LV peak +dp/dt in healthy dogs. It has also been shown to increase with the progression of clinical signs in dogs with MVD due to a shortening of the ejection time. However, in moderate to severe MR, isovolumic contraction and relaxation times can be extremely short or non-existent due to the presence of an opening in the mitral valve area. Therefore, in that case, the TEI index seems to be inaccurate for assessing myocardial function.

Information provided by spectral Doppler recordings of systolic MR and diastolic transmitral flow

Continuous-wave Doppler trace of systolic MR
Mitrval regurgitation flow profile, assessed by continuous-wave Doppler mode, reflects LA pressure, systolic LV function, preload as well as systemic arterial pressure. The peak velocity of a holosystolic MR is usually between 5 and 6 m/s (corresponding to a maximum systolic LV–LA pressure gradient of 100 mmHg or slightly higher, according to the Bernoulli equation). Systolic LV impairment and high LA pressure (as well as systemic arterial hypotension) may result in a decreased peak MR velocity (Figs. IX and X – Data available in Supplemental Data on-line; Fig. 7). Other changes include pointed and/or asymmetric flow profiles (Fig. IX – Data available in Supplemental Data on-line) and the presence of a cut-off sign in mid to late systole (Fig. 7), reflecting a decrease in MR flow due to high LA pressure. Lastly, some authors propose a method to calculate +dp/dt (which is decreased in case of systolic dysfunction) using MR flow profiles (Fig. X – Data available in Supplemental Data on-line).
Pulsed-wave Doppler trace of transmitral flow

The normal transmitral flow profile, assessed by pulsed-wave Doppler mode and recorded at the mitral leaflet tips, is characterized by an early E wave and a late A diastolic wave related to atrial contraction, with an E/A ratio >1 and decreasing with age. In one study performed on 100 healthy dogs, values for E and A were 0.87 ± 0.13 m/s [0.58–1.17] and 0.61 ± 0.12 m/s [0.39–0.86], respectively. The transmitral flow profile reflects diastolic function (relaxation and compliance, volume and recoil) as well as LV filling pressure. A high velocity E wave (>1.5 m/s) suggests elevated LA pressure (Fig. XI — Data available in Supplemental Data on-line). A high velocity E wave with a shorter E deceleration time (<80 ms in dogs older than 10–12 years) is suggestive of the association of high LA pressure and non-compliant LV. Conversely an E/A ratio <1 and/or a prolonged E deceleration time indicates impaired relaxation (Fig. 8A). Several studies demonstrated that high velocity E wave or high E/A ratio are associated with higher risk of death or decompensation in dogs with MVD. As elevated LA pressure and impaired relaxation have opposite effects on the E value, a “pseudo-normal” filling pattern with a normal E/A ratio may be observed when the 2 abnormalities are combined (Fig. 8B and C). In other words, an abnormal relaxation may mask high LA pressure.

As myocardial and annular velocities are less load-dependent than mitral E wave, the E/E' ratio has been proposed to “correct” this effect and predict filling pressure (with E' defined as the early longitudinal mitral annular velocity). E' decreases in the case of impaired relaxation and is usually assessed using the pulsed-wave TDI mode (Fig. XII — Data available in Supplemental Data on-line). An E/E' ratio >9 has been shown to indicate a 95% probability for LA pressure to be >20 mmHg in a canine model of acute MR, and a ratio >12 along with a high E wave velocity can predict the presence of congestive heart failure on thoracic radiographs in spontaneously diseased dogs. Similarly, in another study E/ E' in dogs with MVD and congestive heart failure was significantly higher than in those with compensated MVD, and an E/E' cut-off value of 13 could be used to identify congestive heart failure with a sensitivity and a specificity of 80% and 83%, respectively. However, E' is not totally load-independent. As volume overload markedly increases with severe MR, the E/E' ratio becomes of limited relevance (except in the case of impaired relaxation and subsequent reduced E').

Other conventional Doppler variables

Assessment of the pulmonary venous flow profile is of limited value in dogs with MVD, as MR may enter the pulmonary veins and contribute to noisy profiles of poor quality. Conversely, calculation of the isovolumic relaxation time (IVRT, defined as the time interval from the Doppler signal of aortic valve closure to the beginning of the mitral E wave) and assessment of peak E/IVRT may be of interest as these variables have been shown experimentally to be correlated with LA pressure and LV end-diastolic pressure in the dog. A decrease in IVRT is suggestive of increased filling pressure. According to Schober et al., an E/IVRT ratio >2.5 and an IVRT <45 ms in dogs with moderate to severe chronic MR are usually associated with the presence of congestive heart failure on thoracic radiographs.

Pulmonary arterial hypertension

Pulmonary arterial hypertension is defined as high diastolic or systolic pulmonary arterial pressure, a condition that may lead to right ventricular and atrial enlargement, followed by right-sided heart failure. Systolic and diastolic pulmonary arterial pressure can be evaluated non-invasively...
by Doppler assessment of tricuspid valve regurgitation or pulmonic valve regurgitation, respectively (see examples in Fig. XIII — Data available in Supplemental Data on-line). 8,16,18 In dogs with MVD, both severity and prevalence of Doppler-derived evidence of PAH have been shown to increase significantly with heart failure class (prevalence of 27% and 72% for ISACHC class II and III, respectively). 18 However, PAH may also be present at early stages of the disease even in dogs belonging to ISACHC classes 1a and 1b if MVD is associated with moderate to severe MR. 18 This again illustrates the potential interest of performing echocardiographic examinations on dogs with MVD but no clinical signs. Systolic pulmonary arterial pressure has also been shown to be a prognostic factor for survival or disease worsening in dogs with symptomatic MVD and also a prognostic factor for decompensation in dogs with asymptomatic MVD. 14,23

One limitation of the method used to assess PAH is that it relies on Doppler measurement of pulmonic and tricuspid regurgitations, which may be absent or insufficient for determining pulmonary arterial pressure. In that case, "surrogate" variables may be used to compensate this drawback and predict the presence of PAH, including the main pulmonary arterial diameter to Ao diameter ratio (MPA/Ao), the pulmonary flow acceleration time (AT), the acceleration to ejection time ratio (AT/ET), and lastly the Tei index of right ventricular function. A significant correlation between systolic pulmonary arterial pressure and all these conventional echo-Doppler variables

Figure 8  Pulsed-wave Doppler traces of transmitral flow in 2 dogs with mitral valve disease and diastolic dysfunction. 8A: In this dog (with mild mitral regurgitation), the transmitral flow profile shows an alteration of the relaxation phase with an E/A ratio less than 1. 63 8B and 8C: This dog has severe mitral regurgitation associated with diastolic dysfunction, thus explaining that the transmitral flow profile is normal ("pseudonormal" filling pattern, Fig. 8B). However, tissue Doppler imaging (here two-dimensional color mode) of the left ventricular free wall confirms a marked diastolic dysfunction for both radial (here shown) and longitudinal motion with an E′/A′ ratio lower than 1. Fig. 8C displays a simultaneous recording of myocardial velocities in a sub-endocardial (yellow) and sub-epicardial (green) segment of the left ventricular free wall. S′, E′, and A′ are the peak myocardial velocities during systole, early diastole, and late diastole, respectively. AVC: aortic valve closure and AVO: aortic valve opening (assessed from the pulsed-wave Doppler trace of the systolic aortic flow).
(positive correlation for MPA/Ao and the Tei index, and negative for the others), has been demonstrated in the dog.\textsuperscript{68} In the same study, systolic as well as diastolic right myocardial TDI alterations were demonstrated to be associated with PAH, even for mild increases in pulmonary arterial pressure (Fig. XIV — Data available in Supplemental Data on-line).\textsuperscript{66} Thus any alteration of right myocardial function using TDI may raise the suspicion of systolic PAH in dogs with MVD and no measurable tricuspid regurgitation, although factors other than pulmonary arterial pressure can influence right TDI variables (e.g., primary right systolic dysfunction).

Recent echocardiographic techniques (tissue Doppler imaging, strain and strain rate imaging, speckle tracking echocardiography)

Tissue Doppler imaging

Tissue Doppler imaging is a relatively recently developed ultrasound technique which allows the quantification of both global and regional myocardial function from measurements of myocardial velocities in real time (see reference 29 for review). Annular velocities can also be quantified using the TDI technique. The pulsed-wave TDI mode provides information on tissue movements from a single sample volume. As shown in Fig. XII (Data available in Supplemental Data on-line), the pulsed-wave TDI mode is currently used mainly to assess the early diastolic E’ wave at the mitral valve annulus, in order to calculate the mitral E wave/E’ ratio.\textsuperscript{22,63–67} The 2D color TDI mode is better than the pulsed-wave TDI mode for the evaluation of myocardial function because of its ability to simultaneously quantify velocities in several segments within a single myocardial wall or within different myocardial walls in order to calculate velocity gradients (Figs. 9 and 10) and to assess intra- or interventricular synchrony, respectively (Fig. 11). The TDI technique has been shown to be more sensitive than conventional echocardiography in detecting systolic and diastolic myocardial alterations in humans as well as in experimental or spontaneous heart diseases in animals, as demonstrated by our group in a dog model of dilated cardiomyopathy.\textsuperscript{29,69} One important TDI application

![Figure 9](image-url)  
**Figure 9** Longitudinal myocardial velocity profiles of the left ventricular free wall (LVFW) obtained from a dog with moderate mitral valve disease using two-dimensional color tissue Doppler imaging (left parasternal 4-chamber view). Simultaneous recordings of myocardial velocities are obtained in 2 segments of the LVFW (basal and apical segments, yellow and green curves respectively). A typical severe longitudinal dysfunction is observed, characterized in both segments by an inverted E/A ratio. A positive post-systolic contraction wave (PSC), confirmed by Strain Imaging (data not shown), occurring after aortic valve closure and greater than the S wave, is also present for the apical motion. The color display of velocity is superimposed on the two-dimensional view (left upper panel). S, E, and A are peak myocardial velocities during systole, early diastole, and late diastole, respectively. LA: left atrium. LV: left ventricle.
Figure 10  Radial velocity profiles recorded within 2 segments of the left ventricular free wall using the two-dimensional color tissue Doppler imaging (TDI) mode in 2 Cavalier King Charles Spaniels with severe mitral valve disease but "opposite" systolic myocardial performance (right parasternal transventricular short-axis views). These 2 simultaneous recordings of myocardial velocities in a sub-endocardial (yellow) and sub-epicardial (green) segment both indicate that the sub-endocardium is moving more rapidly than the sub-epicardium in systole and also in diastole, thus defining systolic and diastolic myocardial velocity gradients (white double arrows). However, for the dog in Fig. 10B, the sub-endocardial and sub-epicardial velocity profiles are nearly superimposed in systole, thus indicating a very low systolic myocardial velocity gradient (0.9 cm/s versus 3.9 cm/s in Fig. 10A; for comparison values obtained in a population of 100 healthy dogs were 2.5 ± 0.8 cm/s).45 Systolic dysfunction of the dog from Fig. 10B was not "overt" using conventional echocardiography (fractional shortening of 35%, i.e., within normal ranges). The dog in Fig. 10A is characterized by a radial hyperkinetic state, which was confirmed using Strain and Strain Rate imaging (see Figs. 12 and 13). AVC: aortic valve closure and AVO: aortic valve opening (assessed from the pulsed-wave Doppler trace of the systolic aortic flow). See Fig. 9 for remainder of key.
is the assessment of diastolic function, which may be impaired in aged dogs with MVD (Figs. 8 and 9). Such diastolic alterations are usually more common and more pronounced for the longitudinal than for the radial motion (personal observations). However, in one recent study, no decrease in radial or longitudinal early diastolic velocities or in TDI E/A ratio (suggesting an impaired diastolic function) was observed in dogs with MVD compared to healthy controls. Conversely several diastolic TDI variables (i.e., early TDI diastolic wave (E) and TDI E/A ratio in different segments) were significantly increased in dogs with congestive heart failure compared with those without any sign of decompen-sation and normal controls. However, the former had a significantly higher heart rate than the latter, which may have contributed to these diastolic findings to an unknown extent. In addition, although TDI variables are less load-dependent than conventional echocardiographic indices, a preload influence is highly likely, as a significant correlation has been found between the LA/Ao ratio and early diastolic velocities. Recent data from human studies have confirmed that both systolic and diastolic TDI velocities of the LV are preload-dependent. Alteration of myocardial synchrony may also be observed in dogs with MVD, using left parasternal long-axis views (Fig. 11). Tidholm et al. demonstrated that the difference in longitudinal systolic velocity time-to-peak between the LV and the interventricular septum was significantly increased in dogs with MVD, with and without congestive heart failure, as compared to healthy control dogs, indicating intraventricular dyssynchrony. Whether such alteration is primarily related to MVD or represents an age-related finding remains however to be determined.

Lastly, as shown in Fig. 10, the TDI technique may also be used to help identify systolic changes, revealing increased systolic velocities and gradients in the case of hyperkinesia and the opposite pattern in the case of hypokinesia. Systolic transmural gradients should be preferred because they are more reliable and sensitive indicators of regional LV dysfunction than isolated systolic velocity values. In the study by Tidholm et al., no decrease in systolic performance (but instead an increase in several systolic velocities) was evidenced in dogs with MVD using the TDI technique. Again a load effect and an influence of heart rate may partially explain these results.
Strain and Strain Rate imaging

Strain and Strain Rate imaging are 2 quantitative TDI-derived imaging techniques, which can be used to measure myocardial segmental deformation (contraction or stretching) and rate of deformation, respectively.29,72 Myocardial strain represents the deformation of a myocardial segment over time, and is expressed as the % change from its original dimension. Myocardial strain rate (expressed in s\(^{-1}\)) is the temporal derivative of strain, and therefore describes the rate of myocardial deformation. Unlike TDI, Strain and Strain Rate imaging provide true measures of local myocardial deformation, thereby separating active from passive myocardial motion and offering a more “representative” or direct evaluation of intrinsic myocardial function. Figs. 12 and 13 show examples of increased systolic function assessed by strain and strain rate imaging in a dog with MVD. Very few data are available regarding strain and strain rate alterations associated with canine MVD.70 This is why preliminary results are presented here of an ongoing prospective study being performed at our unit, which is designed to assess radial and longitudinal systolic myocardial function in canine MVD using several ultrasound techniques including Strain imaging. For this purpose 74 dogs from different breeds with MVD were prospectively recruited between 2006 and 2011. Dogs receiving an inotropic drug (pimobendan) were excluded from the study. As expected, this MVD Group was mostly composed of males (n = 53, 72%), aged adult small-breed dogs (10.1 ± 1.7 years, range: 6.5–12.7 years), with an overrepresentation (49/74, 66%) of English Toy Spaniels (n = 24), Yorkshire Terriers (n = 9), Bichons (n = 8) and Poodles (n = 8). Forty-seven of the 74 MVD dogs (64%) received one or more treatments for heart failure at the time of diagnosis. Treatments included angiotensin converting enzyme inhibitors such as benazepril, enalapril, imidapril, and ramipril (44 dogs [59%]), furosemide (20 dogs [27%]), and spironolactone (19 dogs [26%]). Additionally, 17 healthy small-breed dogs matched for body weight (9.6 ± 4.8 kg, range: 2.0–18.5 kg) and age (9.0 ± 1.5 years, range: 7.0–11.5 years) were recruited during the same period. Strain imaging examinations were performed by the same trained observer (VC), as previously described and validated by our group, using an ultrasound unit.
Figure 13  Example of radial hyperkinesia confirmed by regional radial strain rate recorded within the left ventricular free wall from a dog with moderate mitral valve disease (same dog as in Figs. 10A and 12, right parasternal transventricular short-axis view). The strain rate profile (expressed in $s^{-1}$) is positive during systole (SRS), indicating regional thickening, and then features 2 negative diastolic peaks during early filling and atrial contraction (SRE and SRA) corresponding to a biphasic thinning phase. The SRS value is high (9.2 $s^{-1}$) compared to values obtained in a population of healthy dogs (5.8 ± 1.1%). The color display of strain rate is superimposed on the right parasternal transventricular short-axis view (left upper panel). Strain length = 8 mm. Region of interest size = 5/3 mm. See Fig. 12 for remainder of key.

Figure 14  Box plots representing minimal values, 25th, 50th, 75th percentiles, and maximal values of radial (14A) and longitudinal strain (14B) assessed in healthy dogs ($n = 17$) and in 74 age- and body-weight-matched dogs with mitral valve disease from different heart failure classes (ISACHC class 1, 2 and 3; $n = 37$, $n = 22$ and $n = 15$ respectively). Compared to healthy dogs (control group), diseased dogs (MVD group) are characterized by a wide range of radial and longitudinal strain values, particularly in ISACHC class 2. Additionally, a significant decrease in absolute value of longitudinal systolic strain is observed in dogs from ISACHC class 3 (16.1 ± 6.7%) as compared with healthy dogs (22.9 ± 5.1%) and dogs from the ISACHC class 1 (24.6 ± 5.1%) and 2 (21.9 ± 6.0%). *, $P < 0.01$ versus control group; †, $P < 0.001$ versus ISACHC class 1; ‡, $P < 0.001$ versus ISACHC class 2.
Figure 15  Longitudinal strain profiles recorded at the base of the left ventricular free wall using Strain imaging in 2 King Charles Spaniels with mitral valve disease and different longitudinal myocardial function (from the left para-sternal 4-chamber view). For both dogs, the longitudinal strain profiles are negative, confirming a regional compression (i.e., myocardial shortening) during systole and then a regional diastolic expansion. The dog from Fig. 15A shows a normal longitudinal strain profile, maximal at the time of AVC (StS) with a normal StS value (−2.3%; for comparison, values obtained in a population of healthy dogs were −25.5 ± 3.6%). Conversely, the dog from Fig. 15B shows an abnormal longitudinal strain profile characterized by a very low absolute value of peak strain (StS) between AVO and AVC (−10%). The maximal longitudinal deformation occurs after AVC indicating the presence of a post-systolic contraction wave (PSC). Moreover, the systolic shortening is preceded by an early systolic lengthening (yellow stars). The color display of strain is superimposed on the left para-sternal 4-chamber view (left upper panel of Fig. 15A). Strain length = 12 mm. Region of interest size = 5/3 mm. AVC: aortic valve closure and AVO: aortic valve opening (assessed from the pulsed-wave Doppler trace of the systolic aortic flow). LA: left atrium. LV: left ventricle. RA: right atrium. RV: right ventricle.
Radial systolic LV strain was measured between the 2 papillary muscles by using the right parasternal ventricular short-axis view and longitudinal systolic LV strain was measured at the base using the left apical 4-chamber view. As shown in Fig. 14, no significant difference in radial strain was observed between dogs with MVD and healthy controls. Conversely, a significant decrease in the longitudinal absolute value of systolic strain was identified at the latest heart failure stage (ISACHC class 3) compared with healthy controls and dogs from other ISACHC classes (Figs. 14 and 15). These results are in accordance with those described in humans with non-ischemic MR showing that deformation imaging techniques are more sensitive than conventional ones to detect systolic alteration.26,51 Interestingly, our study also shows a marked variability of strain values in the MVD group, and particularly in heart failure dogs with a wide overlap of values, suggesting that systolic changes (including both hyper- and hypokinesia) associated with canine MVD are highly dependent on the individual and cannot be predicted solely from the ISACHC failure class.

Speckle tracking echocardiography

Two-dimensional STE is the most recently developed ultrasound technique and allows quantitative
assessment of regional myocardial function. This non-Doppler technique is based on frame-by-frame tracking of the tiny echo-dense speckles observed within the myocardium on gray scale 2D echocardiographic images and subsequent measurement of myocardial motion. By analyzing speckle motion, STE offers the opportunity to assess myocardial tissue velocity, strain and strain rate, as well as the LV rotation independently of cardiac translation and beam angle, unlike the Doppler-based techniques (TDI or TDI-derived techniques). The STE technique may be used to assess systolic strain and regional synchrony in canine MVD. An example of longitudinal systolic strain alteration, identified by STE in a dog with MVD, is presented in Fig. 16. Longitudinal systolic strain may also be assessed by STE for the whole LV in 18 different segments using 3 different standard apical planes (Fig. 17). The obtained bull’s-eye representation of segmental systolic strain has been found to be closely correlated with coronary anatomy in humans.

Conclusion

In conclusion, conventional echo-Doppler examination provides an accurate diagnosis of canine MVD and of its consequences on cardiac remodeling, LV function and cardiovascular pressures. Serial echo-Doppler examinations can therefore be recommended in dogs with MVD in order to identify and track these alterations over time and detect an ongoing worsening of the disease. Additionally, in asymptomatic MVD dogs, several standard echo-Doppler variables have been shown to be related to clinical outcome and may help in predicting animals at risk for decompensation. As performed in our lab, serial measurements of these combined variables over time can also therefore be recommended in asymptomatic dogs (at least once a year, according to the case), as they can allow an early detection of dogs at risk for rapid progression into congestive heart failure (which could represent a rationale for a closer monitoring and early treatment prescription). These measurements mainly include grading of MR severity, evaluation of pulmonary arterial pressures, assessment of filling pressures and left heart changes (LA/Ao, FS%, LV diameters, LV volumes and corresponding ESVI and EF% using a planimetric method). Nevertheless, further studies in large canine populations are needed to determine breed-by-breed reference intervals for some these parameters (e.g., the planimetric ones) and to investigate the effect of heart rate, age, concomitant treatment or blood volume status. Further prospective studies using STE are also needed to confirm our results regarding the deterioration of systolic longitudinal strain at the latest stage of the disease, to analyze myocardial synchrony changes and determine the influence of such alterations on clinical outcome and therapeutic strategy.

Conflict of interest

None.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jvc.2011.11.005.
References


