Mitral valve prolapse in Cavalier King Charles Spaniel: A review and case study

Changbaig Hyun

Victor Chang Cardiac Research Institute, 384 Victoria St. Darlinghurst, Sydney, NSW 2010, Australia

A 5 year-old spayed female Cavalier King Charles Spaniel was presented after a 3- to 5-day onset of severe respiratory distress. The dog also had a history of several episodes of syncope prior to presentation. A comprehensive diagnostic investigation revealed a midsystolic click sound on cardiac auscultation, signs of left sided cardiac enlargement in ECG and thoracic radiography, mitral valvular leaflet protrusion into left the atrium, decreased E-point-to septal separation (EPSS) and mitral regurgitated flow in echocardiography, all of which are characteristic signs of mitral valvular prolapse. After intensive care with antidiuretics and a vasodilator with oxygen supplement, the condition of the dog was stabilized. The dog was then released and is being medicated with angiotensin converting enzyme (ACE) inhibitor with regular follow-up.

Key words: Cavalier King Charles Spaniel, mitral valve prolapse, valvular endocardiosis, heart

Introduction

Mitral valve prolapse of the Cavalier King Charles Spaniel (MVP-CKCS) is characterized by valvular insufficiency due to abnormal myxomatous accumulation and nodular changes on valvular leaflets of the left atrioventricular valve [5,28]. For the last decade, there has been a dramatic increase in its prevalence in this dog breed [2]. Retrospective studies on auscultatory findings on MVP-CKCS revealed a prevalence of 11.4-44.95%. Heart murmur was age and sex-dependent [28,34]. Similar degenerative valvular disease, also known as chronic valvular fibrosis, myxomatous valvular degeneration, valvular endocardiosis, has been reported in other dog breeds, especially in small and deep-chested breed such as Miniature Poodles, Miniature Schnauzers, Chihuahuas, Dachshunds and small terriers [3,19,28]. This disease accounts for about 75% of all heart disease cases in dogs [6]. The tricuspid valves can be also affected, less frequently [28]. While valvular disease in other dog breed becomes increasingly prevalent as dogs get older, MVP-CKCS is showing the disease at a much younger age, with around 19% of dogs under 1 year of age having a heart murmur, and probably more than 50% of 5 year of age having murmurs [10].

MVP-CKCS is an idiopathic disease with evidence of polygenic inheritance in Cavalier King Charles Spaniels (CKS) and 1.5 times more prevalent in male dogs [10,30]. Although there is no known aetiology for this disease, genetic defect in hyaluronic acid signalling for epithelial-mesenchymal transformation in endocardial cushion formation may involve in the pathogenesis. In human, MVP is genetically heterogeneous and is inherited as an autosomal dominant exhibiting age and sex dependent penetrance. Although two genetic loci have been mapped at 16p121-p11.2 and Xq28 [8,32], the actual causative gene has not been found yet.

MVP-CKCS is a slowly progressive disease and do not show any detectable signs in early stage of disease process [12]. As the disease progresses, an abnormal myxomatous accumulation on valvular leaflets causes nodular degeneration on valvular tissue, often extending to chordae tendineae [4,17]. The valve is then prolapsed into the left atrium, leading to a midsystolic click sound. The disease is eventually progressed to significant valvular distortion, leading to hemodynamic changes due to valvular insufficiency and regurgitation concurrent with left side heart enlargement. The entire process can take many years and can be ended in congestive heart failure, although the affected dogs can die suddenly.

Mitral valvular regurgitation (reverse blood flow from the high pressure ventricle to the low pressure atrial chamber) is characteristic in MVP-CKCS [3,24,28]. The determinants of regurgitant volume and disease severity include: regurgitant orifice size, pressure differences between left atrium and ventricle, and time from onset of contraction to opening of the aortic valve [15]. Severe mitral regurgitation (MR) causes LV volume overload, which can lead to left heart
failure. MR also predisposes to cardiac arrhythmias, especially those originating in the dilated atrium. However, many dogs have severe cardiomegaly but minimal clinical signs, because atrial compliance (distensibility) increases as the regurgitant volume gradually increases [14].

The main clinical signs of MVP-CKCS are attributable to cardiac disease or left-sided heart failure and include exercise tolerance, progressive cough or tachypnea, and syncope. Cough is the clinical sign that is observed most commonly in dogs with clinically evident mitral regurgitation. Syncope is a particularly important and may be related to insufficient forward flow, pulmonary hypertension or arrhythmias [25,28].

Although the physical examination findings may vary depending on the progress of disease, a systolic murmur with a characteristic midsystolic click sound (due to mitral valve prolapse) can be audible over the mitral area and left apex. Sometimes precordial thrill can be palpable over the left apex.

P mitrale (long duration of P wave), P pulmonale (increased amplitude of P wave) and sinus arrhythmia are common finding in ECG. Progressive cardiomegaly with left-sided enlargement is a predominant finding in routine thoracic radiography. As the disease progresses, generalized cardiomegaly, left mainstem bronchial compression, and pulmonary venous distension are obvious. Due to pulmonary oedema, overall lung density (interstitial and alveolar infiltrates) can be increased especially, in the perihilar lung zones. These infiltrates are characteristically dorsal and bilaterally symmetric; however, oedema may be worse in the right caudal lobe.

Echocardiography sometimes provides the definitive evidence for MVP-CKCS. In four-chamber view at mitral valve level, the prolapsed and thickened mitral valve and enlarged left atrium can be observed, although it is not clear in the early stage of disease [21]. Furthermore, in the same echocardiographic view, regurgitated mitral blood flow can be also observed in colour-Doppler echocardiography [7, 34]. M-mode echocardiography will provide cardiac measurement, which is useful to determine the disease progress and prognosis [21]. Due to nodular degeneration on valvular leaflets, valvular tip may locate closer to interventricular septum, causing shortening of EPSS (E point to septal separation) and decreased F slope (implying decreased blood flow in mitral orifice). As the left atrium is enlarged, LA/Ao ratio (left atrium/Aorta ratio) may increase. However, the left ventricle may be normal, increased or decreased in size, depending on the amount of mitral regurgitation. Therefore, fractional shortening (FS) may also vary. The clinical laboratory tests will be useful to differentiate extracardiac disorders such as Cushing’s disease, renal failure, and the effects of drug therapy [29]. However, there will be no pathognomic haematological and biochemical changes indicating MVP-CKCS, although high prevalence rate of thrombocytopenia with enlarged platelets (giant platelet) in this dog breed has been reported [32]. However, the association is not clear. In human with familial mitral prolapse, high prevalence rate of haemophilia has also been reported [28].

The differential diagnosis of MVP-CKCS includes dilated cardiomyopathy, congenital AV valve malformations, bacterial endocarditis and primary respiratory diseases.

Unfortunately, there is currently no practical way of curing the disease, although valvular replacement by surgical method is being used in human. However it is simply not practical in dogs. Therefore treatment is aimed at ameliorating the existing signs. Treatment will depend upon the grade of murmur and clinical signs. Treatment of the asymptomatic dog with a murmur is not recommended unless there is evidence of impending heart failure such as gross cardiomegaly and pulmonary venous distension.

Initial therapy for MVP-CKCS showing signs of congestive heart failure or pulmonary oedema includes antiuretics for reducing ventricular preload and eliminating pulmonary fluid accumulation; vasodilators for reducing vascular afterload and oxygen supply for improving ventilation. Dietary modification to low salt diet and exercise restriction will be required. However, restrictive low salt diet is not necessary for dog having early stage of MVP-CKCS. Dietary supplements such as fish oil and enzyme Q may be beneficial, although the effect of these supplements has not be proven. Baseline home therapy of MVP-CKCS involves angiotensin converting enzyme (ACE) inhibitor and antiuretics, and sometimes digitalis.

Prognosis will vary depending on the stage of disease. Dogs with low-grade murmur may survive for several years without therapy. Although the intensity of murmur is generally correlated with the disease progress, some dogs with severe murmur may survive longer than dogs with moderate murmur.

Materials and Methods

Animal

A 5 year-old spayed female Cavalier King Charles Spaniel, weighing 5.7 kg, was presented several weeks after a 3- to 5-day history of severe respiratory distress.

Diagnostic work-ups

Haematology and blood chemistry was done using a Roche ABX blood cell counter (Cobras Minos Vet, Roche diagnostic System, Germany) and, a Cobas Mira system (Roche Diagnostic Systems, Germany) using Boehringer Mannheim reagents (Germany), respectively. Phonocardiographic assessment was done at the point of maximal intensity (PMI) using amplified stethoscope (I-stethos, Androscope™, USA) with analysing software (STG®, Stethographics, USA). A 6-lead system electrocardiographic assessment
Mitral valve prolapse in Cavalier King Charles Spaniel: A review and case study

(Space Labs Inc, model 90603A, Redmond, USA) was performed with the patient in lateral recumbency. Thoracic radiographs were taken as described elsewhere [13]. Echocardiographic and colour Doppler studies (Acuson 128 XP10, Acuson Corporation, Mountainview, USA) were undertaken with the patient in a standing position.

Results

History and Physical examination

The dog was referred with the chief complaints of dyspnea, tachypnea, and events of syncope. The first and second syncopes occurred 10 and 3 months prior to presentation, respectively. Furthermore the dog had experienced several syncopes in the past month associated with either excitement or vigorous exercise (i.e. running). Respiratory distress was worsen over the last 2-3 days so that the dog could not sleep in lateral recumbency and showed non-productive retching. Cough and dyspnea were the main clinical features in this dog. The cough was deep and resonant. It was more prominent at night and after exercise or excitement. The dog was anorexic, especially after recovering from the recent syncope.

Electrocardiogram and phonocardiogram

In cardiac auscultation, an early to mid-systolic murmur with mid click sound was auscultated at the left cardiac apex, while S1 and S2 are still clearly audible (Fig. 1A). The amplitude of S1 heart sound was also increased. These findings suggested mitral valvular stenosis or regurgitation due to valvular defect. Lung sound was normal.

Six lead electrocardiograph showed P mitrale (0.06 sec) and P pulmonale (0.05 mV) with left QRS axis deviation (between −0° and −30°). There was mild sinus arrhythmia with irregular ventricular rhythm, although QRS duration (0.05 sec) was normal (Fig 1B). This result implied left atrial enlargement.

Thoracic radiography

In a lateral view of thoracic radiograph, it was obvious that left atrial and left ventricular shadow were enlarged with marked increased density in the perihilar region (pulmonary over-circulation). Although the caudal border of the heart was obscured by diaphragmatic lung lobe, the outline of the caudal vena cava and the thoracic aorta was distended. Pulmonary vein was wider than pulmonary artery due to pulmonary overcirculation (Fig. 2A). In a dorsoventral view, the cardiac shadow was enlarged. In the lung lobe, markedly increased parenchymal density and peribronchial pattern with air bronchogram were suggestive for pulmonary oedema (Fig. 2B). Overall radiographic signs implied a severe left atrial and left ventricular enlargement with pulmonary oedema, which might be caused by congestive heart failure due to valvular defect.

Echocardiogram and Doppler studies

In right parasternal long axis two-chamber view of echocardiogram, the hinge point of two mitral valve leaflets was displaced caudally and its leaflet was protruded from the mitral annular plane extending into the left atrium (Fig. 3A). In M-mode echocardiogram, the septal and left ventricular posterior wall motion was accentuated. EPSS (E-point-to septal separation) was remarkably shortened due to abnormally thickened and distorted anterior mitral valve. Decreased F-slope implied the reduction in mitral blood flow caused by valvular insufficiency (Fig 3B). Increased LA/Ao ratio indicated left atrial enlargement. Mildly increased left ventricular wall thickness systole and diastole (LVWs and LVWd) with decreased left ventricular diameter at diastole (LVIDd) indicated mild hypertrophic left ventricle (Table 1). In colour flow Doppler echocardiogram, severe regurgitated turbulence was observed between the left atrium and ventricle. The large regurgitated jet flow occupied almost 70% of left atrium (Fig. 4A). In pulsed-wave Doppler echocardiography, the systolic signal is present both above and below the baseline, resulting in directional ambiguity and inability to determine peak velocity, and shows a wide band of velocities through systole, indicating turbulent flow (Fig. 4B). Therefore, those findings were strongly indicated mitral valve regurgitation.

Differential diagnosis

The differential diagnosis was made from dilated cardiomyopathy, congenital atrioventricular valve malformations, bacterial endocarditis and tracheal/bronchial collapse.
Because complete blood cell count did not show elevated WBC and any evidence of metastatic inflammation (e.g. polyarthritis, proteinuria), bacterial endocarditis was ruled out. Because no pulmonary crackle sound and dorsal displacement (flattening) of trachea and bronchi were not observed in lung auscultation and thoracic radiographic examination respectively, primary pulmonary diseases and tracheal/bronchial collapses were also ruled out. Because the echocardiogram did not show any abnormal parameter for right ventricular thinning or enlargement, dilated cardiomyopathy was also ruled out. The characteristic midsystolic click sound in cardiac auscultation, the sign of left side heart enlargement in ECG and thoracic radiography and characteristic turbulent flow at mitral annular plane in echocardiogram indicated the mitral valvular endocardiosis.

**Treatment and follow-up**

To reduce ventricular preload and remove fluid excess from pulmonary vasculature, furosemide (Lasix®) was
Mitral valve prolapse in Cavalier King Charles Spaniel: A review and case study

administered intravenously, 2 mg/kg in every 1 hr, till respiratory discomfort was stabilized. With concurrent antidiuretic therapy, sodium nitroprusside was infused at 2 µg/kg/min for 2 hrs to reduce vascular afterload. Oxygen was supplied via intranasal tube to improve respiratory ventilation. Blood pressure and cardiac rhythm was monitored initially every 30 min while sodium nitroprusside was infused, then monitored every 1 hr until the patient condition was stabilized. Renal function (plasma urea nitrogen and creatinine) was also monitored every day. After two-day intensive care, the patient respiratory and cardiac condition was returned to normal, although the murmur was still auscultated from the left side heart. The dog was then released from the intensive care unit. The dog was treated with antidiuretics (furosemide, 3 mg/kg BID) and ACE inhibitor (enalapril, 0.5 mg/kg BID). A diet modification (low sodium diet, fish oil and enzyme Q supplement) and exercise restriction was recommended to owner. A month later, the dog was clinically re-evaluated and did not show any respiratory distress, such as coughing and retching. Renal function was evaluated and was found to be normal. Administration of furosemide was discontinued and enalapril was replaced to benazapril (0.5 mg/kg SID). The follow-up thoracic radiography and echocardiography in this dog are undergoing on 3 months interval.

Discussion

MVP-CKCS usually occurs in young dogs, while similar valvular diseases occur in elderly dogs in other breed dogs. In this case, the dog presumably had clinical signs much earlier than the first presentation, based on previous history of syncope and severity of disease shown. This case was diagnosed as a MVP with severe MR as shown by characteristic clinical signs that include a midsystolic murmur, left side heart enlargement, and valvular protrusion with mitral regurgitation.

Diagnostic criteria for MVP-CKCS including similar chronic valvular disease was established based on the intensity of femoral artery pulse [31], intensity of cardiac murmur [11], and degree of mitral valvular protrusion into left atrium [23]. In study for diagnostic correlation between the intensity of femoral artery pulse and severity of MVP, there was an inverse relationship between pulse strength and heart rate, degree of obesity and MVP severity in CKCS and Dachshunds, which are two breeds predisposed to MVP [19,23]. However, the measurement of femoral artery pulse is too subjective, thus it may be differed by the skill and experience of examiner [24]. Another problem for this criterion is that it may be also differed by the animal’s body fat thickness and hydration state.

Another study showed that the intensity of the systolic cardiac murmur, assessed by auscultation (grade 1-6), was correlated to the severity of valvular degeneration and to the echocardiographic dimensions of the heart (LA/Ao ratio and LVIDd) [11]. A shortening of total electromechanical systole (Q-S2), S1-S2 (phonocardiogram) intervals and ratio of the amplitudes of S1 and S2 were also correlated with the severity of heart failure. This study indicated the likelihood of diagnosing the disease by cardiac auscultation increases with the increasing degree of MR. However, mild MR is usually associated with relatively short lived early systolic murmur, which means it may be undetectable, unlike severe MR with strongly audible holosystolic murmur. As noticed in femoral artery pulse study, cardiac auscultation is also affected by examiner’s experience [24]. Furthermore it is sometimes difficult to differentiate from innocent/physiological murmur associated with a high-flow state.

Using echocardiographic examination, Pedersen et al. [23] proposed a better way to predict the disease progress in MVP-CKCS. In this study, the degree of leaflet protrusion, the leaflet thickness and the degree of MR (size of jet lesion by colour-Doppler mapping) were well correlated with the
severity of MR. In human, the thickness of the valvar leaflets is an important prognostic marker [23]. This method is advantageous for determining the disease state over other methods described above [16], especially in case with mild MR. Despite its accuracy, it requires high skill and knowledge of echocardiography. Therefore this method is not practically applicable in private practice.

In this study, the dog had an easily detectable femoral artery pulse, although it had strongly audible systolic murmur with midsystolic click sound. This finding suggests the prognosis may be different based on the method used. Echocardiographic measurement with colour Doppler mapping showed the dog had severe MR and advanced left side heart enlargement with moderately thickened and distorted valvar leaflets suggesting severe state of MVP. Therefore, the intensity of femoral artery pulse may not be a good indicator of disease state as noticed in this study.

MVP-CKCS is often associated with thrombocytopenia (giant platelet disease) [9,20,26]. Furthermore, CKCS often has a decreased concentration of plasma nitric oxide metabolites and a decreased serum magnesium concentration [22,27], which are known to be associated with human endothelial dysfunction [1,18]. However, this dog did not show any abnormalities in haematology and blood chemistry.

ACE inhibitors are commonly used in management of mitral valvular diseases. As a preventive and protective remedy, ACE inhibitors are well known and widely used to control variety of human heart diseases. However, two drug trial studies for MVP-CKCS failed to identify a clear benefit from early use of ACE inhibitor in dogs having no clinical signs. However, once clinical evidence of heart failure is obvious, use of ACE inhibitor is demandable in the absence of significant pre-existing renal disease or excessive concurrent diuretic use.

In this case, ACE inhibitor was very effective in delaying the disease progression. At the early stage of treatment, ACE inhibitor was used with antiduretics. However, the dog was gradually anorexic due to hypokalemia after increased renal excretion. Therefore, the antiduretics was discontinued and replaced to more potent single dose ACE inhibitor (Benazapril). This case study found that the use of antiduretics for reducing ventricular preload is not necessary, if ACE inhibitor is administered or if pulmonary oedema does not exist.

The affected dogs normally can survive for 3-4 years after the development of a cardiac murmur. The length of survival is entirely depended on the quality of follow-up (e.g. regular base health check, dietary modification and symptomatic medication). This dog is still alive and healthy since two years has been passed after the first episode of syncope. Because the cardiac performance is substantially reduced and the ventricular hypertrophy (dilation) extends to right ventricle, digitalis is being administered with ACE inhibitor in this dog.

In this case report, a dog with severe respiratory distress and couple of syncope was present. Using a comprehensive diagnostic investigation, mitral valve prolapse with severe mitral regurgitation was reached as the final diagnosis. After short period of intensive care with an antiduretics, a vasodilator and an oxygen supply, the dog was released with a prescription of ACE inhibitor and recommendations of dietary modification and exercise restriction.

References

Mitral valve prolapse in Cavalier King Charles Spaniel: A review and case study