The Prevalence of Pulmonary Hypertension in Cavalier King Charles Spaniels Compared with Other Breeds with Myxomatous Mitral Valve Disease

Siddharth Sudunagunta BVetMeda, Daniel Green BVScb, Rob Christley BVSc, PhDc, Joanna Dukes-McEwan BVMS, MVM PhDa

aCardiology Service, Small Animal Teaching Hospital, Institute of Veterinary Science, University of Liverpool, Neston, CH64 7TE, UK

bWaikanae Beach, Wellington, 5036, New Zealand

cDepartment of Epidemiology and Population Health, Institute of Infection and Global Health, University of Liverpool, Neston, CH64 7TE, UK

Corresponding author: ssudun@liv.ac.uk (S. Sudunagunta)

Running title: Prevalence of PH in CKCS with MMVD

**Abstract**

**Introduction:** Pulmonary hypertension (PH) is a common consequence of myxomatous mitral valve disease (MMVD). Cavalier King Charles Spaniels (CKCS) are frequently affected by MMVD, and appear to have different disease progression compared to other small breed dogs. The aim of this study was to determine if CKCS are more likely to develop PH as a result of MMVD than dogs of other breeds. A secondary aim was to explore whether breed or the presence of PH impacted upon survival.

**Animals:** 187 dogs diagnosed with MMVD retrieved from electronic patient records, 94 CKCS and 93 non-CKCS.

**Methods:** Retrospective review of dogs with MMVD in ACVIM stage B2, C or D. Data were analyzed for presence of PH, congestive heart failure (CHF), selected echocardiographic variables including mitral E wave velocity (E vel) to isovolumic relaxation time ratio (E/IVRT) and were compared between CKCS/non-CKCS and dogs with/without PH. Survival analysis was also performed.

**Results:** ACVIM stage (p < 0.001), CKCS (p = 0.005), left atrium-to-aortic ratio (LA/Ao) (p < 0.001), E vel (p < 0.001) and log10(E/IVRT) (p < 0.001) were significant at the univariate level for the development of PH. At the multivariate level only ACVIM stage remained significant (p = 0.044), suggesting worsening MMVD was the predominant determinant of PH development in this study. Pulmonary hypertension was associated with greater likelihood of CHF (p < 0.001) and death (both cardiac (p < 0.001) and all-cause mortality (p = 0.011)). Cavalier King Charles Spaniels were more likely to experience cardiac death than non-CKCS (p = 0.004).

**Conclusions:** In this study development of PH was associated with worse MMVD, according to ACVIM stage

**Keywords:** Canine; tricuspid regurgitation; post-capillary pulmonary hypertension; Degenerative valvular disease

Abbreviations

|  |  |
| --- | --- |
| ACVIM | American College of Veterinary Internal Medicine |
| AF | Atrial Fibrillation |
| CKCS | Cavalier King Charles Spaniel |
| E vel | Transmitral E wave velocity |
| E/IVRT  | Ratio of E wave velocity to isovolumic relaxation time |
| ESVI  | End-systolic volume index |
| LA  | Left atrium |
| LA/Ao  | Left atrium to aortic ratio |
| L-CHF  | Left-sided congestive heart failure |
| LVIDDn | Left ventricular internal diameter in diastole, indexed for bodyweight |
| LVIDSn | Left ventricular internal diameter in diastole, indexed for bodyweight |
| MMVD  | Myxomatous mitral valve disease |
| PH  | Pulmonary hypertension |
| PR | Pulmonic regurgitation |
| R-CHF  | Right-sided congestive heart failure |
| TR  | Tricuspid regurgitation |

Introduction

Myxomatous mitral valve disease (MMVD) is the most common acquired heart disease in dogs [1,2]. Cavalier King Charles Spaniels (CKCS) are affected at an earlier age than other breeds [1,3-6]. Cavalier King Charles Spaniels have been found to be more likely to die as a result of their heart disease [3,6-10], though one large study found CKCS had a longer time to reach the end point (cardiac death) than non-CKCS [1,2,11].

Pulmonary hypertension (PH), defined in animals as pulmonary arterial systolic pressure greater than approximately 30 mmHg [1,3-6,12] is divided into five categories: 1) pulmonary arterial hypertension; 2) pulmonary hypertension due to increased left sided filling pressures associated with left heart disease, e.g. MMVD; 3) pulmonary hypertension due to pulmonary disease and/or hypoxia; 4) pulmonary hypertension due to thromboembolic disease; 5) miscellaneous [3,6-10,12,13].

Right heart catheterization is the gold standard method of diagnosing PH, but is rarely performed in clinical practice as it is invasive and requires sedation/anaesthesia [12]. Therefore PH is most commonly diagnosed by measurement of the velocity of the tricuspid regurgitation (TR) jet, which can be used to determine the pressure gradient between the right ventricle and right atrium, via the modified Bernoulli equation (pressure gradient = 4v2, where v is the velocity of the regurgitant jet). This provides an estimate of systolic pulmonary artery pressure [12], after exclusion of pulmonic stenosis. Diastolic pulmonary artery pressure is estimated in the same fashion, using the velocity of pulmonic regurgitation (PR) [12].

Left heart disease is one of the most common causes of PH in dogs [14]; the reported prevalence of PH in dogs with MMVD varies between 13-71% [15-19]. Increased left atrial pressure results in increased pulmonary venous and capillary pressures that results in elevated pulmonary arterial pressure [14]. This may be exacerbated by reactive, hypoxia-induced, pulmonary arterial vasoconstriction [14]. While dogs with asymptomatic MMVD are unlikely to have severe PH [1,2] the severity and prevalence of PH increases with severity of MMVD [18,20] and is associated with a poorer prognosis [15,20]. It is not known why some dogs with MMVD develop PH and others do not.

To the authors’ knowledge there have been no studies showing an association between dog breed and development of PH secondary to MMVD. We hypothesized that CKCS with MMVD seen at our hospital had a greater prevalence of PH than dogs of other breeds with MMVD.

The primary aim of this study was to determine whether CKCS were more likely to develop PH than non-CKCS in dogs with MMVD and to explore which variables may be associated with development of PH.

As a secondary aim, we explored whether breed (CKCS yes/no) or the presence of PH impacted upon survival, for both all cause and cardiac mortality.

Materials and methods

The study was approved by the Veterinary Research Ethics Committee, University of Liverpool (reference: VREC503).

This was a retrospective data analysis project. The echocardiography analysis and archiving softwared of the cardiology service of the Small Animal Teaching Hospital, University of Liverpool, was searched for dogs coded ‘MMVD’ (myxomatous mitral valve disease) over the period of 2008–2016. Echocardiograms were performed by ECVIM-CA (Cardiology) diplomates or residents in training working under their supervision. Measurements were taken off-line by the diplomate/resident in question. An average of three consective R-R intervals was used for measurements (five if the patient was in atrial fibrillation (AF)). Patients were gently manually restrained in right and left lateral recumbency. All echocardiograms were performed without sedation. Dogs eligible for inclusion were: 1) five years of age or older; 2) body weight < 20 kg; 3) echocardiographic diagnosis of MMVD, defined as nodular lesions on the mitral valve, with or without prolapse and mitral regurgitation on color Doppler; 4) evidence of cardiac remodeling changes (ACVIM Stage B2, C or D [21]). Left-sided CHF (L-CHF) was diagnosed based on clinical signs, the presence of pulmonary venous congestion and cardiogenic pulmonary oedema seen on thoracic radiographs, and/or an improvement in clinical signs following furosemide administration in a patient with advanced MMVD seen echocardiographically. Right-sided CHF (R-CHF) was defined by the presence of ascites, pleural effusion or small volume pericardial effusion in the absence of other conditions that may have been responsible. Patients were considered to be in stage D of their disease if they were refractory to high doses of furosemide (8 – 12 mg/kg/day) and had therefore been prescribed torasemide and/or hydrochlorothiazide. As all dogs had been referred by a primary veterinarian, some dogs had been treated with furosemide, benazepril and pimobendan to stabilize the patient prior to the initial echocardiogram. Dogs without structural heart changes due to MMVD or without remodelling (i.e. ACVIM Stages A, B1) and those with PH due to other causes were excluded. Dogs with other structural heart disease (e.g. congenital) were also excluded. Dogs with concurrent cardiac disease, either congenital or acquired (e.g. dilated cardiomyopathy, endocarditis), were excluded. Dogs with known concurrent respiratory disease seen on thoracic imaging (computed tomography, radiography or tracheobronchoscopy) (e.g. neoplasia, idiopathic pulmonary fibrosis, pneumonia), or significant systemic disease that may have affected pulmonary pressures (e.g. angiostrongylosis) were also excluded. Dogs were not excluded if they had AF, as it was most likely to be a consequence of their MMVD. From the computerized hospital recordse the following information was retrieved: date of birth; breed; gender; body weight, medications received. From the echocardiography records, the following data were obtained: left atrium to aortic ratio (LA/Ao) measured from the right parasternal short axis two-dimensional views at end-diastole, optimizing LA size [22], M-mode left ventricular internal diameter in diastole and systole, indexed for body weight by allometric scaling (LVIDDn and LVIDSn) [23], TR velocity (from left apical view optimizing the right heart) and peak PR velocity (from either right or left cranial short axis views, whichever optimized the PR) [12, 14]. Pulmonary hypertension was defined as TR ≥ 2.8 m/s with or without PR ≥ 2.2m/s [12,14,15]. As an estimate of left sided filling pressures, mitral E wave velocity, isovolumic relaxation time and E wave to isovolumic relaxation time ratio (E/IVRT) data were retrieved [12,19], having been acquired from left apical four and five chamber views. From images obtained from the right parasternal long axis four chamber view optimizing left ventricular length and area, the end-systolic left ventricular volume, derived by Simpson’s method of discs [24] indexed to body surface area (ESVI), was retrieved in order to estimate left ventricular systolic function, with values > 30 mL/m2 considered to be consistent with systolic dysfunction [25,26]. For dogs with multiple echocardiographic examinations, the visit associated with the highest TR velocity was used.

Survival analysis

Where possible, outcome data were obtained from clinical records. Otherwise, primary veterinary practices were contacted. Death was defined as cardiac (euthanasia due to progressive cardiac disease or sudden cardiac death) or all cause mortality (cardiac death plus death due to all other causes).

Statistical analysis

Statistical analysis was performed using commercially available softwaref,g. Normality of data distribution was determined using Shapiro-Wilk tests. Age in years and transmitral E wave velocity within ACVIM subgroups B2 and C were normally distributed and were represented as mean [standard deviation] and were compared between CKCS/non-CKCS and PH/non-PH using an independent t test. There were only three non-CKCS stage D dogs and therefore statistical analysis was not performed on this group. Tricuspid regurgitation velocity was normally distributed and is represented as mean ± standard deviation and was compared across ACVIM classes of heart disease using a one way ANOVA with Bonferroni correction applied to assess statistical significance for post hoc analysis. No other data were normally distributed; therefore continuous data (body weight; LA/Ao TR velocity for PH patients; PR; transmitral E wave velocity; E/IVRT, end systolic volume index (ESVI), LVIDDn and LVIDSn) are represented as median [range] and were compared using a Mann-Whitney U test. Categorical data (gender; presence of PH (y/n); mean peak PR > 2.2m/s (y/n); breed = CKCS (y/n); presence of CHF (y/n); PH prevalence within ACVIM class; ESVI > 30 mL/m2) were compared using chi-squared tests. The prevalence of AF between CKCS/non-CKCS and PH/non-PH was determined using a Fishers exact test, due to low numbers.
Univariate and multivariate analysis were performed using backwards logistic regression to assess for the effects of individual factors on the development of PH (age, breed [CKCS/non-CKCS]), ACVIM stage, LA/Ao, transmitral E wave velocity, log10 (E/IVRT)). Values which were significant at the univariate level (p < 0.2) were used in the multivariate model.
Survival time was assessed on all-cause mortality and cardiac mortality using Kaplan Meier curves and log-rank analysis. A value of p < 0.05 was considered statistically significant.

Results

A total of 187 dogs met the inclusion criteria for the study. There were 94 CKCS and 93 non-CKCS (Table 1). The breeds represented in the non-CKCS group were: 19 cross breeds, ten Chihuahuas, eight cocker spaniels, six Yorkshire terriers, five Bichon frisés and four or fewer of the following: miniature schnauzer, Japanese spitz, border collie, whippet, Maltese, Jack Russell terrier, lurcher, griffon Bruxellois, Norfolk terrier, Shetland sheepdog, dachshund, Airedale, Tibetan terrier, Lancashire heeler, Scottish terrier, shih tzu, toy poodle, Staffordshire bull terrier, Lhasa apso, Irish terrier, King Charles spaniel, Hungarian hound, Pekingese; beagle. One hundred and nine dogs were male, 78 female.

The rest of the signalment, key echocardiographic variables and presence of L-CHF data are shown in Table 1.

There was no difference in age, weight or gender between CKCS and non-CKCS dogs. Eight dogs had AF at the time of inclusion in the study, three CKCS and five non-CKCS (p = 1.00).

The dogs were in different stages of their disease, and as such were being treated with a variety of cardiac medications: furosemide (n = 66), pimobendan (77), spironolactone (51), benazepril (68), torasemide (2), hydrochlorothiazide-amiloride (5), digoxin (3), diltiazem (3), amlodipine (3), aspirin (2), clopidogrel (3), sildenafil (4), ramipril (1), codeine (1) and sotalol (4). Combinations of medications are provided in Table 2 (supplemental data, available online). One hundred and one dogs were not receiving any medications. Fourteen dogs were in R-CHF, 11 CKCS and three non-CKCS, with two cross breed dogs and one Staffordshire bull terrier.

Left atrium to aortic ratio (p = 0.036), transmitral E wave velocity (p = 0.011) and E/IVRT (p = 0.01) were significantly higher in CKCS (Table 1). E wave velocity and E/IVRT were not significantly different within ACVIM groups when comparing CKCS and non-CKCS.

Pulmonary hypertension was more prevalent in CKCS than non-CKCS (p = 0.005; Table 1). The dogs with PH had higher LA/Ao (p < 0.001); E wave velocity (p < 0.001) and E/IVRT (p < 0.001) than the dogs without PH (Table 3).

The prevalence of PH did not differ within ACVIM stage for CKCS/non-CKCS (Table 4, available as supplemental data online). All dogs in stage D (12 CKCS and three non-CKCS) had PH. Six of the eight dogs with AF had PH (p=1.00). No dog had isolated diastolic PH (i.e. PR > 2.2 m/s in the absence of TR > 2.8 m/s).

The mean TR velocity across all dogs was 3.4 m/s, and was significantly higher for CKCS (3.52 m/s [0.77 - 5.66 m/s]) compared to non-CKCS (3.25 m/s [1.54 - 4.68 m/s]; p=0.031; Figure 1). There was no difference in TR velocity within ACVIM stage between CKCS and non-CKCS (data not shown). Of the 102 dogs with L-CHF, 82 had PH (80.1 %), either at the time of the examination, or previously diagnosed and controlled on medication. Twelve out of fourteen dogs with R-CHF had PH. The mean TR velocity was significantly lower in all dogs in stage B2 (mean: 2.84 ± 0.64 m/s) compared to stage C (mean: 3.4 ± 0.72 m/s) or D (mean: 3.94 ± 0.75 m/s; p<0.001 for both), and was lower in dogs in stage C compared to D (p=0.023 after correction) (Figure 2).

Pulmonic regurgitation could be measured in 96 dogs; 55 CKCS and 41 non-CKCS. The median PR velocity was higher in CKCS (p = 0.01; Table 1). Twenty-four CKCS and six non-CKCS had peak PR > 2.2m/s (p = 0.02); all of these patients had systolic PH as well.

A total of 74/185 (40 %) dogs had reduced systolic function, as defined by an ESVI > 30mL/m2. There was no difference in the ESVI between CKCS/non-CKCS (p = 0.151; Table 1) or PH/non-PH dogs (p = 0.162; Table 2), and the number of dogs with systolic dysfunction did not differ across groups (Tables 1 and 2). LVIDDn was greater in both CKCS and dogs with PH (p < 0.001 for both), while LVIDSn did not differ between CKCS/non-CKCS (p = 0.937) or PH/non-PH (p = 0.234; Tables 1 and 2).

Logistic regression found ACVIM stage (p < 0.001); CKCS (p = 0.005); LA/Ao (p< 0.001); E vel (p<0.001) and log10(E/IVRT) (p < 0.001) to be significant at the univariate level for the development of PH. At the multivariate level only ACVIM stage remained significant (p = 0.044).

Survival analysis:

A total of 130/187 dogs were dead at the time the study was conducted (all cause mortality). There was no difference in all cause mortality between CKCS and non-CKCS (p = 0.086; Figure 3). Dogs with PH were more likely to die than those without PH (p = 0.011; Figure 4).

Eighty-seven dogs died or were euthanized due to cardiac disease: CKCS were significantly more likely to die a cardiac death (p = 0.004; figure 3). Dogs with PH were significantly more likely to die a cardiac death (p < 0.001; figure 4); dogs without PH were unlikely to experience a cardiac death, with fewer than 50% reaching this endpoint.

A total of 43/187 dogs died or were euthanized due to non-cardiac disease. Causes of death included neoplasia (lymphoma, mast cell tumour, haemangiosarcoma, mass of unconfirmed diagnosis), chronic kidney disease, neurological disease (seizures, intervertebral disc disease), gastrointestinal disease (chronic diarrhoea, pancreatitis), intra/postoperative complications, immune-mediated haemolytic anaemia, or a combination of multiple co-morbidities. For 12 patients the cause of death was not clear from communications with the owners or referring veterinary surgeon.

Discussion

In this study univariate analysis indicated a positive association between breed (CKCS) and the development of PH. However, breed did not remain significant at the multivariate level. Multivariate logistic regression showed that ACVIM stage to be the primary determinant in the development of PH in dogs with MMVD, suggesting that these patients had post-capillary PH, at least predominantly, due to chronically elevated left atrial pressures [12,14]. This is in accordance with previous findings [18,20]. It may be that LA/Ao and E/IVRT were ‘intervening variables’, i.e. related causally to the process by which disease severity causes PH. Progression from stage B2 to C to D by definition requires development of increased LA size and pressure [2,12,19], which is a key determinant in the development of post-capillary PH [12-14]. Patients that have progressed to stage C and D have been exposed to greater LA pressures for a prolonged period of time, which would allow more time for vascular remodeling and PH development [14].

There were more stage D CKCS than non-CKCS, which may in part explain the greater prevalence of PH among CKCS in this population. It is not clear from this study if the higher number of stage D CKCS represents a propensity for the breed to progress more rapidly to severe stages of the disease and die earlier, which would be in agreement with the findings by Serfass et al. [8]. Alternately CKCS have a longer overall survival, or are better able to tolerate severe CHF, and are therefore more likely to gradually develop CHF that is refractory to high furosemide doses. The latter theory is potentially in agreement with the findings of QUEST [11], which found that CKCS had a longer time to reach the endpoint of their study (cardiac death, euthanasia due to CHF or treatment failure). In our study population all cases were not enrolled in this study at the time of MMVD diagnosis, but the point at which their TR velocity was greatest and as such, we cannot comment on the overall disease progression time.

The LA/Ao was significantly larger in CKCS than non-CKCS, which may in part explain why neither breed nor LA/Ao were significant at the multivariate level for PH development. It may be due to the fact that there were more stage D CKCS than non-CKCS. The LA/Ao was also significantly larger in dogs with PH than those without.

The prevalence of PH in this study of dogs with MMVD was 65.8%, which is in keeping with previously published findings [15-17,19]. It should be noted that the current study excluded dogs with mild MMVD (stage B1), which was not the case in some other studies; therefore these studies may have had a lower prevalence by virtue of having relatively fewer patients with more advanced disease. For example Serres et al [18] found PH in 13.9% of patients with MMVD across all ISACHC classes.

Cavalier King Charles Spaniels overall had a higher median E/IVRT; however within a given ACVIM class this was not the case, suggesting that dogs at the same disease stage had similar filling pressures. The high number of CKCS in stage D is likely responsible for the overall difference in E/IVRT between the groups. The differences in echocardiographic findings in CKCS compared to non-CKCS may reflect the unique natural history and disease progression seen in this breed [3,15-19,28], which has been hypothesized to be reflected in their different outcomes in numerous veterinary trials. For example, CKCS have previously been shown to develop clinical disease at an early age [3,14,28,29].

It is possible that undiagnosed concurrent disease (for example respiratory conditions such as bronchomalacia, pulmonary vascular disease or pulmonary thromboembolism which are common in small breed MMVD prone dogs [12,15,20,30,31]) may have contributed to PH (combined post-capillary and pre-capillary PH) [13]. Pre- and post-capillary PH are differentiated by measuring pulmonary capillary wedge pressure, an approximation of pulmonary venous and left atrial pressure, which is increased in post-capillary PH [12,13]. This requires right heart catheterization, an invasive procedure that is not routinely performed in small animals. In human medicine, echocardiographic variables and ratios, such as the recently coined ‘echocardiographic pulmonary to left atrial ratio’ [32] have been proposed as a non-invasive surrogate for differentiating between pre- and post-capillary PH, however this has not been evaluated in dogs.

Dogs with PH were more likely to be in L-CHF. This is to be expected, as increasing LA pressures are associated with both PH and L-CHF. It should, however, be noted that 40 (33%) dogs with PH did not have overt CHF, i.e. were in stage B2. Previous studies have found a PH prevalence of 19.9 - 47% in asymptomatic (either ISACHC class II or ACVIM stage B2) dogs with MMVD [18,20]. In this population, the B2 dogs with PH comprised of 22 CKCS (59.4%) and 18 non-CKCS (38.3%), with possible over-representation of B2 CKCS with PH, though this did not achieve statistical significance.

Tricuspid regurgitation velocity, and therefore systolic PH severity, increased with MMVD severity, in terms of ACVIM class. Dogs in stage B2 had lower TR velocities than those in stage C, who in turn had lower TR velocities than stage D dogs. This finding is in agreement with other published literature showing a correlation between PH severity and heart disease severity [18,20].

End-systolic volume index and LVIDSn were not significantly different between CKCS and non-CKCS or between dogs with and without PH, suggesting that left ventricular systolic function did not differ significantly between those groups (although both the CKCS group and the PH group had larger LVIDDn). Systolic function is difficult to quantify in dogs with MMVD, as the reduced afterload provided by the MR allows for normal or even hyperkinetic measurements of traditional systolic function variables, such as fractional shortening or ejection fraction. End-systolic volume index has been found to be increased in dogs with CHF due to MMVD [25,26]. Using ESVI > 30mL/m2 as a cutoff, 74 dogs in this study had systolic dysfunction. There was no difference in number of CKCS/non-CKCS or PH/non-PH dogs with systolic dysfunction, suggesting that LV systolic function is not associated with the development of PH in dogs with MMVD.

With regards to the survival analysis, it is important to remember that the starting point of the study was the time at which the highest TR value was documented. Therefore, the time to death was not from the first documented instance of PH, but from its peak severity. This study was not designed to thoroughly evaluate the progression of PH and its effects on survival, but more to observe the progression from the point at which PH was most severe echocardiographically. Furthermore, some patients were lost to follow up for survival analysis. Survival analysis was a secondary aim of the study; the authors primarily sought to establish whether prevalence of PH was greater for CKCS than dogs of other breeds.

Dogs with PH were more likely to experience cardiac or all cause death. Pulmonary hypertenion has been found to be a poor prognostic indicator in dogs with and without MMVD, particularly if the TR pressure gradient exceeds 55 mmHg [11,16,33-35].

In this study, CKCS were more likely to experience a cardiac death than non-CKCS; there was no difference in all cause mortality between the two groups. This is in contrast to studies by Häggström et al. (2008) and Pouchelon et al. (2008), both of which reported a longer survival time in the CKCS group [11,36].

This was a retrospective study and is therefore subject to the limitations inherent to such studies. There was no standardization with regards case assessment, diagnostic investigations or treatment. For example, there was no strict furosemide cut-off dose before switching to torasemide; in the hospital torasemide is administered in patients already receiving 8 - 12mg/kg furosemide per day. Pre-existing medications may have affected echo measurements, in particular furosemide, pimobendan and sildenafil. Inter- and intra-observer variation for echocardiographic measurements was not assessed. The study was conducted in a referral population, and therefore may not represent the general population as a whole. While efforts were made to exclude concurrent systemic or other respiratory disease, it is possible that some cases had underlying conditions that were undiagnosed, e.g. neoplasia, thromboembolic disease, angiostrongylosis, idiopathic fibrosis, etc. [12,14,15,35]. Having said that, the fact that PH prevalence and severity increased with ACVIM stage, along with the strong association with MMVD severity markers (LA/Ao; E velocity; E/IVRT) supports our presumption that MMVD contributed significantly to the development of PH.
Pulmonary hypertension was not diagnosed by direct pulmonary arterial catheterization. This is considered the gold standard; however is not routinely used in veterinary medicine, as it is invasive, expensive and requires general anesthesia. Tricuspid regurgitation velocity is used as standard by veterinarians to diagnose PH [12]. Velocities can be underestimated due to imperfect alignment of the Doppler cursor with the flow of the regurgitant jet.

Similarly, 12/14 dogs in R-CHF had PH; PH is known to predispose to R-CHF development [2,14] and these patients would have had increased right atrial pressure and possibly reduced right ventricular systolic function, which would have reduced the TR velocity, leading to underestimation of the PH [14,27]. However, one study has found that adding estimated right atrial pressures is of little additional value [37]. Additionally, sometimes TR/PR are not present and therefore cannot be measured [38]. Right ventricular systolic function was not routinely assessed (e.g. by tricuspid annular plane systolic excursion [39]) in these patients. Eight patients had AF, which may have affected the measurement of the transmitral E wave velocity, as the values can be more variable. This should be mitigated as we performed more measurements on dogs with AF (five rather than three), to obtain mean values.

Conclusions:

In this study population of dogs with MMVD, CKCS were more likely to have PH than non-CKCS dogs, although multiple logistic regression indicated that the only significant determinant of PH was ACVIM stage of disease, i.e. severity of MMVD and chronicity of elevated LA pressures. Further studies are needed to determine the causative mechanism for PH development in CKCS with MMVD. In this study population, CKCS were found to be more likely to experience a cardiac death than non-CKCS. Dogs with PH were more likely to die, both in terms of all cause mortality and cardiac death.

Acknowledgement

The authors would like to thank Liz Bode for her input in preparation of the manuscript.

Conflict of Interest:

The authors do not have any conflicts of interest to disclose.

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Footnotes:

d GE Echopac version 113, GE Medical Systems, Buckinghamshire, UK

e Tristan Veterinary Practice Management Solution, version 1.8.3.1110

f SPSS Statistics Version 24, IBM

g GraphPad Prism Version 7; GraphPad Software Inc

Table 1: Population characteristics and echocardiographic variables of the 187 dogs in the study, comparing Cavalier King Charles Spaniels (CKCS) and non-CKCS

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All Dogs** | **CKCS** | **Non CKCS** | **p value (CKCS vs non-CKCS)** |
| **Number** | 187 | 94 | 93 | - |
| **Age in years (mean ± SD)** | 9.72 ± 2.32 | 9.72 ± 2.26 | 9.72 ± 2.39 | 0.992 |
| **Weight in kg (median [range])** | 10.2 [1.9-19.8] | 10.2 [5.5-17.1] | 10.2 [1.9-19.8] | 0.397 |
| **Male (number [%])** | 109 [58.3%] | 59 [62.8%] | 50 [53.8%] | 0.212 |
| **PH (number [%])** | 123 [65.8%] | 71 [75.5%] | 52 [55.9%] | **0.005** |
| **LA/Ao (median [range])** | 1.94 [1.19-3.53] | 2.03 [1.21-3.44] | 1.91 [1.19-3.53] | **0.036** |
| **TR velocity in m/s (median [range])** | 3.4 [0.77-5.66] | 3.52 [0.77-5.66] | 3.25 [1.54-4.68] | **0.031** |
| **PR velocity in m/s (median [range]); data only available for 96 dogs** | 1.81 [0.31-3.8] | 1.95 [0.31-3.8] | 1.49 [0.69-3.25] | **0.01** |
| **Transmitral E wave velocity in m/s (median [range])** | 1.17 [0.49-2.41] | 1.24 [0.51-2.41] | 1.06 [0.49-1.99] | **0.011** |
| **E/IVRT (median [range])** | 1.89 [0.51-21.50] | 2.13 [0.63-21.50] | 1.67 [0.51-6.60] | **0.01** |
| **ESVI in mL/m2****(median [range]; data only available for 185 dogs)** | 26.8 [7.3-94.5] | 27.1 [7.3-94.5] | 24.9 [7.5-83.9] | 0.151 |
| **ESVI > 30m****mL/m2 (number [%]; data only available for 185 dogs)** | 74 [40%] | 36 [39%] | 38 [41%] | 0.81 |
| **LVIDDn (median [range])** | 1.97 [1.32-2.99] | 2.08 [1.48-2.99] | 1.88 [1.48-2.69] | **<0.001** |
| **LVIDSn (median [range])** | 1.07 [0.48-1.88] | 1.11 [0.48-1.88] | 1.03 [0.58-1.64] | 0.937 |
| **L-CHF (number[%])** | 103 [55.1%] | 57 [60.6%] | 46 [48.4%]  | 0.093 |

Abbreviations: E/IVRT: E wave velocity to isovolumic relaxation time ratio; ESVI: end-systolic volume index; LA/Ao: left atrium to aortic ratio; L-CHF: left-sided congestive heart failure; LVIDDn: left ventricular internal diameter in diastole, indexed for body weight; LVIDSn: left ventricular internal diameter in systole, indexed for body weight; PH: pulmonary hypertension; PR: pulmonic regurgitation; SD: standard deviation; TR: tricuspid regurgitation

Table 2: (Supplemental) Combinations of medications received by the 187 dogs prior to inclusion in the study

|  |  |
| --- | --- |
| **Drug(s)** | **Number of dogs** |
| None | 101 |
| Furosemide, benazepril, pimobendan, spironolactone | 32 |
| Furosemide, benazepril, pimobendan | 9 |
| Pimobendan | 9 |
| Furosemide, pimobendan | 5 |
| Furosemide, benazepril | 3 |
| Benazepril | 3 |
| Other (two or fewer dogs on treatment combination) | 25 |

Table 3: Population characteristics and echocardiographic variables of the 187 dogs in the study, comparing dogs with and without pulmonary hypertension (PH).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All Dogs** | **PH** | **Non PH** | **p value****(PH vs non PH)** |
| **Number** | 187 | 123 | 64 | - |
| **Age in years (mean ± SD)** | 9.71 ± 2.32 | 9.61 ± 2.31 | 9.93 ± 2.34 | 0.365 |
| **Weight in kg (median [range])** | 10.2 [1.9-19.8] | 10.1 [2.5-19.8] | 10.65 [1.9-19.1] | 0.342 |
| **LA/Ao (median [range])** | 1.94 [1.19-3.53] | 2.09 [1.19-3.53]] | 1.74 [1.33-3.18 | **<0.001** |
| **Male (number [%])** | 109 [58.3%] | 71 [57.7%] | 38 [59.4%] | 0.828 |
| **Transmitral E wave velocity in m/s****(median [range])** | 1.17 [0.49-2.41] | 1.25 [0.49-2.41] | 0.96 [0.51-1.64] | **<0.001** |
| **E/IVRT (median [range])** | 1.89 [0.51-21.50] | 2.25 [0.51-21.50] | 1.39 [0.54-4.46] | **<0.001** |
| **ESVI in mL/m2****(median [range]; data only available for 185 dogs)** | 26.8 [7.3-94.5] | 27.4 [7.3-94.5] | 25.5 [7.5-56.1] | 0.162 |
| **ESVI > 30mL/m2 (number [%]; data only available for 185 dogs)** | 74 [40%] | 53 [44%] | 21 [33%] | 0.147 |
| **LVIDDn (median [range])** | 1.97 [1.32-2.99] | 2.09 [1.32-2.99] | 1.8 [1.48-2.43] | **<0.001** |
| **LVIDSn (median [range])** | 1.07 [0.48-1.88] | 1.07 [0.48-1.88] | 1.08 [0.64-1.41] | 0.234 |
| **L-CHF (number [%])** | 103 [55.1%] | 82 [66.7%] | 20 [31.3%] | **<0.001** |

Abbreviations: E/IVRT: E wave velocity to isovolumic relaxation time ratio; ESVI: end-systolic volume index; LA/Ao: left atrium to aortic ratio; L-CHF: left-sided congestive heart failure; LVIDDn: left ventricular internal diameter in diastole, indexed for body weight; LVIDSn: left ventricular internal diameter in systole, indexed for body weight; PH: pulmonary hypertension; PR: pulmonic regurgitation; SD: standard deviation; TR: tricuspid regurgitation

Table 4: (Supplemental) Chi-squared tests comparing prevalence of pulmonary hypertension in the 187 dogs, separated by ACVIM class

|  |  |  |  |
| --- | --- | --- | --- |
| **ACVIM stage** | **Cavalier King Charles Spaniels (CKCS)** | **Non-CKCS** | **p Value** |
| **B2 (number of dogs with PH/total number)** | 22/37 | 18/47 | 0.054 |
| **C (number of dogs with PH/total number)** | 37/45 | 31/43 | 0.257 |
| **D (number of dogs with PH/total number)** | 12/12 | 3/3 | n/a |

Figure titles and descriptions

Figure 1. Tricuspid regurgitation (TR) velocity compared between Cavalier King Charles Spaniels (CKCS) and non-CKCS. The CKCS group had a significantly higher TR velocity (3.52 m/s [0.77 - 5.66 m/s]) than the non-CKCS group: 3.25 m/s [1.54 - 4.68 m/s])

Figure 2. Tricuspid regurgitation velocity across ACVIM stage. Statistical significance between groups is symbolized as: ★ p<0.05; ★★ p<0.001.

Figure 3. Kaplan-Meier curves to compare survival between Cavalier King Charles Spaniels (CKCS) and non-CKCS. A: All-cause mortality: CKCS median survival: 240 days, non-CKCS median survival: 430 days. B: Cardiac mortality: CKCS median survival: 313 days, non-CKCS median survival: 852 days

Figure 4. Kaplan-Meier curves to compare survival between pulmonary hypertension (PH) and non-PH. A: All-cause mortality: PH median survival: 240 days, non-PH median survival: 535 days. B: Cardiac mortality: PH median survival: 313 days, median survival not calculated for non-PH dogs as event rate <50%.