PAPER

# The occurrence of cardiac abnormalities in canine steroid-responsive meningitis arteritis

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**Objectives:** To document the prevalence of cardiac abnormalities in dogs with steroid-responsive meningitis arteritis and to assess resolution of these abnormalities following corticosteroid therapy.

**Materials and Methods:** Steroid-responsive meningitis arteritis was diagnosed based on signalment, physical examination findings, complete blood count, biochemistry and CSF analysis. Echocardiography, C-reactive protein and cardiac troponin I were measured in all cases before and 10 to 14 days after commencing corticosteroid therapy. Fibrinogen was also measured in a proportion of dogs.

**Results:** Fourteen dogs were prospectively enrolled. Increased cardiac troponin I was identified in five of 14 dogs and echocardiographic abnormalities were detected in 12 of 14 dogs, including spontaneous echo contrast (12 of 14), mild pericardial effusion (five of 14) and mildly decreased fractional shortening (five of 14). All dogs had increased C-reactive protein and fibrinogen was increased in 11 of 12. Corticosteroid treatment was associated with clinical improvement and normalisation of C-reactive protein in all dogs. The cardiac troponin I levels normalised in four of five and fibrinogen had normalised in all five dogs which were retested. Spontaneous echo contrast improved or completely resolved in 12 of 12 and pericardial effusion resolved in five of five dogs. Fractional shortening normalised in two of five dogs.

**Clinical Significance:** Cardiac changes are common in dogs with steroid-responsive meningitis arteritis and most resolve with therapy. Further investigation into the cause and significance of these changes is necessary in determining whether antithrombotic therapy or positive inotropic therapy is indicated.

[Correction added on 20 March 2019, after first online publication: The author names have been corrected to J. Penderis and R Gutierrez-Quintana. The affiliation of G McLauchlan has been changed to Fitzpatrick Referrals - Oncology and Soft Tissue, Surrey GU2 7AJ, UK in the current version.]

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## INTRODUCTION

Steroid-responsive meningitis arteritis (SRMA) is an inflammatory disease of the central nervous system (CNS) that typically affects young dogs (Cizinauskas *et al.* 2000). An immune-mediated aetiology is strongly suspected based on the high titres of IgA documented in both the serum and cerebrospinal fluid (CSF) of affected dogs, the rapid clinical improvement commonly seen following corticosteroid administration and the lack of identification of infectious disease (Maiolini *et al.* 2012). Breed predilection is recognised in numerous breeds, including beagles, boxers and Weimaraners (Harcourt 1978, Poncelet & Balligand 1993, Lowrie *et al.* 2009b). Response to treatment in dogs with SRMA can be monitored by various

 

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methods including repeat CSF analysis or serial measurement of the acute phase protein C-reactive protein (CRP), which is a non-invasive and sensitive marker of clinical remission and a predictive marker of disease relapse (Bathen-Noethen *et al.* 2008, Lowrie *et al.* 2009a).

The co-occurrence of cardiac disease and inflammatory CNS disease in people is recognised. Myocarditis and arrhythmias can occur and are thought to be due to myocyte damage from circulating inflammatory mediators and stimulation of the sympathetic nervous system, respectively (Linde *et al.* 2006). In humans with bacterial meningitis, concurrent myocarditis and purulent pericardial effusion have been reported (Stange *et al.* 2001) along with a reactive pericardial effusion that responded to corticosteroid administration (Berti *et al.* 2013). Pericarditis with a mild effusion is also the most common cardiac manifestation of systemic lupus erythematosus in humans and this resolves with immunosuppressive therapy (Rosenbaum *et al.* 2009). An immune-mediated aetiology has not been proven in dogs with pericardial effusion (Day & Martin 2002).

Cardiac troponin I (cTnI) is extensively used as a marker of cardiac myocyte damage in dogs but has been shown to be non-specific, increasing in various cardiac and non-cardiac conditions (Langhorn & Willesen 2016). Left ventricular systolic dysfunction, pericardial effusion and increased cTnI have been reported in five dogs with SRMA (Covey & Connolly 2018). These patients did not show clinical signs of cardiac disease and their pericardial effusion resolved without therapeutic pericardiocentesis. Epicarditis and myocarditis have also been reported in histopathological examinations of beagles with SRMA as part of a polyarteritis syndrome (Snyder *et al.* 1995). In addition, two separate case reports have documented myocarditis associated with SRMA: based on ECG abnormalities and increased cTnI in one case (Snyder *et al.* 2010), and a pericardial effusion, increased cTnI and spontaneous echocontrast that resolved following treatment of SRMA in another (Navarro-Cubas *et al.* 2011). Neither of these patients presented with clinical signs of cardiac disease.

SRMA can be associated with multi-systemic inflammation and has also been shown to occur concurrently with non-cardiogenic pathological processes including immune-mediated polyarthritis (Webb *et al.* 2002). Panarteritis was reported in laboratory beagles with SRMA (Scott-Moncrieff *et al.* 1992) that underwent *post mortem* examination, revealing necrotising arteritis most commonly involving the small- to medium-sized vessels of the cervical spinal cord, mediastinum and heart.

The primary aim of this study was to document the occurrence of echocardiographic abnormalities and myocardial injury (as documented by increased cTnI) in dogs diagnosed with SRMA. We specifically wanted to assess dogs for spontaneous echocontrast and idiopathic pericardial effusion, while determining whether these dogs had evidence of systemic inflammation by measuring CRP and fibrinogen. The secondary aim was to determine whether any identified cardiac abnormalities resolved as the CRP normalised following corticosteroid therapy.

## MATERIAL AND METHODS

The Ethics Committee at the University of Glasgow approved this prospective study. Dogs referred to the University of Glasgow Small Animal Hospital between April 2014 and April 2015 with clinical signs and signalment compatible with SRMA were eligible for enrolment. Cases that received corticosteroids for the presenting complaint before referral were excluded, as well as patients with any pre-existing concurrent disease diagnosed on history, physical examination or during investigations.

All patients had a detailed clinical history, full physical examination and routine haematology, serum biochemistry and CRP measured. Excess blood was analysed for cTnI and, in some cases, fibrinogen. CRP (Siemens Dimension Xpand Plus, Siemens Healthcare Ltd.) and cTnI (Siemens Immulite 2000, Siemens Healthcare Ltd.) were measured on serum samples and fibrinogen (KC4 Delta Amelung Semi-Automated Coagulation Analyzer, Trinity Biotech) on citrated whole blood at the hospital reference laboratory. Echocardiography was performed in all dogs before anaesthesia for CSF analysis and, or, cervical radiographs as deemed appropriate by the clinician (Lowrie *et al.* 2009b, Maiolini *et al.* 2012). There is no definitive *ante mortem* diagnostic test for SRMA so if these tests were supportive, a presumptive diagnosis of SRMA was made and dogs were treated with glucocorticoids.

The physical examination was performed by a board-certified neurologist and clinical signs suggestive of SRMA were considered to be spinal pain, lethargy and/or pyrexia. The CSF characteristic suggestive of SRMA was sterile neutrophilic pleocytosis. Echocardiography was performed by a board-certified cardiologist or a cardiology resident under the supervision of a board-certified cardiologist, using a GE Vivid 7 echocardiographic system with transducer selection (4, 5 or 10 MHz) depending on the size of the dog. Echocardiographic recordings were made with a simultaneous ECG and all data were stored for analysis. Standard imaging planes were used with the dog restrained in right or left lateral recumbency (Thomas *et al.* 1993). The echocardiographic study was undertaken including 2D, M-mode, spectral and colour Doppler. No tissue Doppler imaging was undertaken. In all patients, echocardiographic measurements were made in two-dimensional mode for calculation of aorta and left atrial diameter and M-mode for left ventricular internal dimension at end-systole (LVIDs), left ventricular internal dimension at end diastole (LVIDd) and fractional shortening (FS). Left atrial diameter, left-ventricular-internal-dimension-at-end-systole and left-ventricular-internal-dimension-at-end-diastole measurements were normalised based on bodyweight as previously described (Cornell *et al.* 2004) before assessment. Pericardial effusion was noted when present and defined as measuring less than 1 cm, with no cardiac tamponade. Spontaneous echo contrast was noted and graded as absent, mild or severe. A single-boarded cardiologist, blinded to cTnI results, reviewed all echocardiograms for the purpose of this study. If possible, echocardiography was performed before administration of any drugs that could influence the results (anaesthetic, sedation or corticosteroids). Blood pressure was not measured in any patient.

Following diagnosis of SRMA, a corticosteroid treatment protocol was initiated as deemed appropriate by the clinician in charge, along with an individualised course of analgesia. Prednisolone therapy was adjusted as previously described (Lowrie *et al.* 2009b). The patients were subsequently discharged once eating and when intravenous analgesia was no longer required.

Repeat evaluation was performed at 10 to 14 days and included neurological examination, echocardiography, CRP and cTnI measurement. In addition, fibrinogen was tested in a proportion of patients.

## RESULTS

### Patients

Fourteen dogs diagnosed with SRMA were included in the study. Breeds represented included four boxers, two beagles, two whippets, three crossbreeds and three other breeds (one Afghan hound, one collie and one miniature poodle). Ten dogs were male (five neutered and five entire) and four were female (one neutered and three entire). The mean age was 12 months (range 6 to 30 months).

### Pre-treatment investigations

All dogs had neutrophilic pleocytosis in the CSF with an increase in nucleated cell count (population median 77 *per* mL, range 12 to 1600; reference <5) without cytological evidence of bacteria. Increased protein was also found on CSF analysis in 11 of 14 patients (population median 485 mg/L, 100 to 1868; reference <250). In addition, 11 of 11 dogs had normal cervical radiographs. On haematology, 11 of 14 dogs showed neutrophilia (population median $14.92 \times 10^9$/L, range 7.12 to 31.25; reference 3 to 11.8) and on biochemistry, six of 14 showed mild hypoalbuminaemia. All dogs had CRP measured before initiating therapy, and this was increased in all 14 patients (median 134 mg/L, range 50 to 243; reference <10). Fibrinogen was measured in 12 of 14 patients only, because of a lack of residual blood in the remaining two. It was increased in 11 of these patients (population median 815 mg/dL, range 350 to 1112; reference <400). Pretreatment cardiac assessment involving cTnI measurement and echocardiography was performed in all dogs. The cTnI was increased in five of 14 dogs (population median 0.1 ng/L, range <0.1 to 14.5; reference <0.15).

One patient was incidentally diagnosed with mild subaortic stenosis with an aortic velocity of 2.46 m/s, reference <2.0 m/s (Boon 2011), without any structural changes noted on echocardiography. Another was sedated with a low dose of 4 µg/kg medetomidine intravenously before referral. Mild left ventricular systolic dysfunction (defined by decreased FS) was noted in five of 14 dogs (population median 27%, range 20 to 36%; reference 24 to 40%). Two dogs had increased normalised left ventricular internal dimension at end-systole (population median 1.11, range 0.79 to 1.35; reference 0.71 to 1.26), and one dog had increased normalised left-ventricular-internal-dimension-at-end-diastole (population median 1.60, range 1.22 to 2.12; reference 1.27 to 1.85). A mildly increased normalised left atrial diameter was noted in six of 14 dogs, although left atrial: aorta ratio was within normal range in all dogs (population median 1.28, range 0.92 to 1.5).

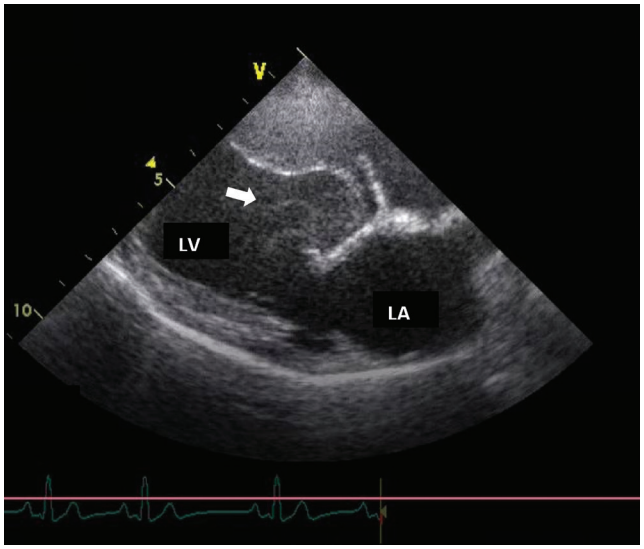


**FIG 1. Right parasternal long-axis view of left atrium (LA) and ventricle (LV) showing (arrow) spontaneous echo contrast (SEC)**

Spontaneous echo contrast (Fig. 1) was found in the left ventricle of 12 of 14 patients and mild pericardial effusion in five of 14. All dogs with increased cTnI had spontaneous echo contrast identified on the echocardiogram. Also, all dogs with pericardial effusion had concurrent spontaneous echo contrast, but only two of five had an increase in cTnI. Two patients with increased fibrinogen had no evidence of spontaneous echo contrast and one patient with spontaneous echo contrast did not have an increase in fibrinogen. Five patients had pericardial effusion and five had decreased FS but only two patients had concurrent pericardial effusion and decreased FS. From descriptive analysis of the results, there appeared to be no relationship between the CRP, cTnI, fibrinogen, FS or normalised left atrial diameter. Tables 1 and 2 summarise the clinicopathological and selected echocardiographic findings before and after treatment.

All dogs were started on therapy with prednisolone, with a total median daily dose of 2 mg/kg (range 0.9 to 2.1) for 2 weeks. In addition, 10 dogs were treated with concurrent omeprazole and two with famotidine. No dogs received cardiac medications or antithrombotic therapy. All dogs received injectable opioid analgesia during hospitalisation and in two dogs, oral tramadol was required for additional analgesia during this period.

### After-treatment investigations

All patients showed significant clinical improvement on reevaluation between 10 and 14 days after starting prednisolone, with complete resolution of signs in 11 of 14 patients and only mild neck pain on manipulation in the remaining three. The CRP was rechecked in all patients and found to be within reference range in 14 of 14. Fibrinogen was repeated in five of 12 cases and was within the normal range in all.

Repeat echocardiography was performed in all 14 patients. Of the five dogs with decreased FS, two normalised, three had

 

**Table 1. Summary of signalment, duration of clinical signs, clinico-pathological findings and echocardiographic abnormalities of each patient**

| Case | Age | Breed | Sex | Duration of signs (days) | Prednisolone dose/day | Neutrophil count (×10⁹/L) RI 3 to 11.8 | Albumin (g/L) RI 29 to 36 | NCC (cells *per* mL) RI <5 | Protein (mg/L) RI <250 | SEC | PE | CRP (mg/L) RI <10 | | Fibrinogen (mg/dL) RI <400 | | CTnI (ng/mL) RI <0.1 to 0.15 | | FS% RI 24 to 40% | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| 1 | 2 year | Boxer | FN | 4 | 0.9 mg/kg | 14.27 | 29 | 65 | **210** | ✓ | × | **132** | **0.4** | * | * | **0.59** | **2.47** | 29 | 23 |
| 2 | 6 months | Boxer | ME | 10 | 1.0 mg/kg | 9.62 | 29 | 750 | **820** | ✓ | ✓ | **121** | **0.7** | * | * | **<0.1** | **<0.1** | 31 | 30 |
| 3 | 1 year | Afghan | ME | 10 | 1.0 mg/kg | 19.22 | 27 | 20 | **750** | ✓ | × | **151** | **6.6** | **717** | **325** | **<0.1** | **<0.1** | **20** | **15** |
| 4 | 8 months | Poodle | MN | 14 | 2.0 mg/kg | 31.25 | 31 | 810 | **990** | × | × | **243** | **78.1** | **810** | **363** | **0.88** | **<0.1** | 28 | 34 |
| 5 | 9 months | Crossbreed | FN | 5 | 2.0 mg/kg | 20.71 | 26 | 88 | **630** | ✓ | × | **228** | **4.2** | **966** | **260** | **<0.1** | **<0.1** | **21** | **15** |
| 6 | 1 year | Golden retriever | MN | 2 | 1.7 mg/kg | 14.28 | 29 | 1600 | **540** | × | × | **136** | **0** | **743** | **287** | **<0.1** | **<0.1** | 25 | 36 |
| 7 | 11 months | Whippet | ME | 7 | 1.3 mg/kg | 15.33 | 36 | 100 | **190** | ✓ | ✓ | **85** | **2.3** | **800** | * | **2.81** | **<0.1** | **21** | 27 |
| 8 | 8 months | Boxer | ME | 1 | 2.0 mg/kg | 7.12 | 26 | 12 | **1560** | ✓ | × | **50** | **0.6** | **900** | * | **<0.1** | **<0.1** | 31 | 35 |
| 9 | 8 months | Crossbreed | MN | 7 | 2.0 mg/kg | 11.97 | 24 | 500 | **430** | ✓ | × | **201** | **1.3** | **1112** | **76** | **14.5** | **<0.1** | 33 | 36 |
| 10 | 1 year | Collie | FE | 10 | 2.1 mg/kg | 18.27 | 27 | 92 | **340** | ✓ | × | **129** | **3.7** | **350** | * | **<0.1** | **<0.1** | **20** | 28 |
| 11 | 2 years | Beagle | MN | 6 | 1.9 mg/kg | 14.51 | 28 | 23 | **160** | ✓ | ✓ | **181** | **2.8** | **613** | * | **2.02** | **<0.1** | **22** | **23** |
| 12 | 9 months | Crossbreed | ME | 3 | 2.0 mg/kg | 18.62 | 28 | 13 | **100** | ✓ | ✓ | **89** | **2.1** | **830** | * | **<0.1** | **<0.1** | 36 | 35 |
| 13 | 9 months | Boxer | MN | 2 | 2.0 mg/kg | 13.93 | 22 | 62 | **1868** | ✓ | × | **170** | **3.8** | **820** | **261** | **<0.1** | **<0.1** | 28 | **22** |
| 14 | 11 months | Whippet | FE | 7 | 2.0 mg/kg | 15.61 | 28 | 13 | **130** | ✓ | ✓ | **126** | **1.8** | **1068** | * | **0.11** | **<0.1** | 33 | **17** |

*not tested. FE female entire, FN female neutered, ME male entire, MN male neutered, RI reference interval, NCC nucleated cell count, SEC spontaneous echo contrast, PE pericardial effusion, CRP C-reactive protein, cTnI cardiac troponin I, FS fractional shortening

**Table 2. Results from selected echocardiographic measurements**

| | FS RI 24 to 40%* | | Normalised LVIDs RI 0.71 to 1.26* | | Normalised LVIDd RI 1.27 to 1.85* | | Normalised LA RI 0.5 to 0.97* | | LA:Ao RI <1.6† | | SEC | | PE | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| 1 | 29 | 23 | 1.07 | 1.25 | 1.62 | 1.76 | 0.97 | 0.94 | 1.45 | 1.4 | ✓ | × | × | × |
| 2 | 31 | 30 | 0.98 | 1 | 1.53 | 1.53 | 0.96 | 0.93 | 1.5 | 1.33 | ✓ | × | ✓ | × |
| 3 | **20** | **15** | 1.22 | **1.33** | 1.63 | 1.67 | 0.89 | **1.03** | 1 | 1.27 | ✓ | ✓ | × | × |
| 4 | 28 | 34 | 0.82 | 0.88 | **1.19** | 1.42 | 0.78 | 0.83 | 0.92 | 1.01 | × | × | × | × |
| 5 | **21** | **15** | 1.19 | **1.33** | 1.61 | 1.68 | **1.04** | **1** | 1.18 | 1.12 | ✓ | ✓ | × | × |
| 6 | 25 | 36 | 0.91 | 0.96 | 1.3 | 1.6 | **1.27** | **1.23** | 1.41 | 1.4 | × | × | × | × |
| 7 | **21** | **27** | **1.34** | 1.13 | 1.8 | 1.63 | **1.07** | **1.12** | 1.31 | 1.39 | ✓ | × | ✓ | × |
| 8† | 31 | 35 | 1.16 | 1.06 | 1.79 | 1.74 | 0.96 | 0.96 | 1.46 | 1.58 | ✓ | × | × | × |
| 9 | 33 | 36 | 0.79 | 0.82 | 1.22 | 1.33 | 0.87 | 0.76 | 1.06 | 0.92 | ✓ | × | × | × |
| 10 | **20** | **28** | 1.22 | 1.03 | 1.62 | 1.5 | **1.01** | **1.05** | 1.27 | 1.4 | ✓ | × | × | × |
| 11 | **22** | **23** | 1.16 | **1.29** | 1.59 | 1.79 | **0.99** | **1.1** | 1.28 | 1.18 | ✓ | × | ✓ | × |
| 12 | 36 | 35 | 0.88 | 0.82 | 1.4 | 1.29 | 0.86 | 0.73 | 1.1 | 0.99 | ✓ | × | ✓ | × |
| 13 | 28 | **22** | 0.88 | 1.02 | 1.32 | 1.41 | 0.79 | 0.86 | 1.21 | 1.36 | ✓ | × | × | × |
| 14 | 33 | **17** | **1.35** | **1.38** | 2.12 | 1.75 | **1.08** | **1.17** | 1.47 | 1.49 | ✓ | ✓ | ✓ | × |

Bold represented results outwith the reference range however on reflection, as the reference ranges are given, this is not needed. RI reference interval, FS fractional shortening, LA left atrial diameter, LA:Ao left atrial to aortic ratio, LVIDs left ventricular internal dimension at end-systole, LVIDd left ventricular internal dimension at end diastole SEC spontaneous echocontrast, PE pericardial effusion

*See Cornell *et al*. (2004)

†See Hansson *et al*. (2002)

†Patient received medetomidine before initial assessment

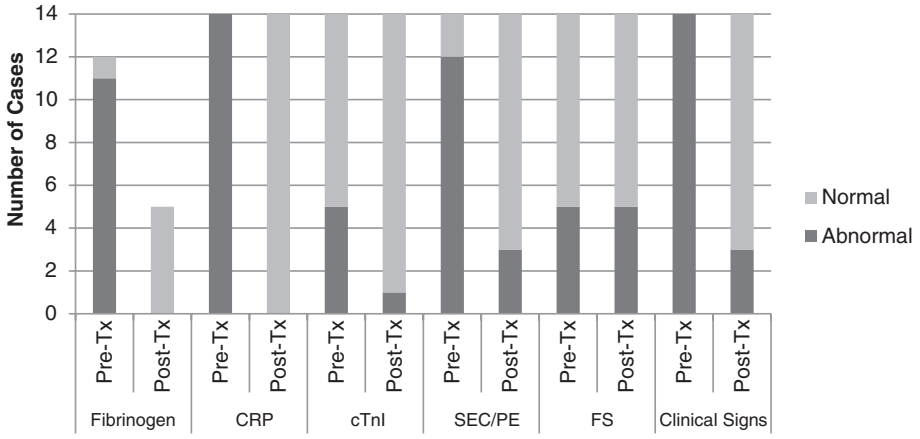


**FIG 2. Comparison of normal and abnormal results before and after treatment of SRMA. CRP C-reactive protein, cTnI cardiac troponin I, SEC spontaneous echo contrast, PE pericardial effusion, FS fractional shortening**

a further reduction in FS and two additional dogs developed reduction in FS (28 to 22% and 33 to 17%). Three dogs developed increased normalised left-ventricular-internal-dimension-at-end-systole, one remained increased and one returned to normal. The spontaneous echo contrast had resolved in nine of 12 patients and was subjectively improved in three of 12 patients. The mild pericardial effusion had completely resolved in five of five patients. Of the six of 12 patients with increased normalised left atrial diameter, four patients showed a mild (<5%) increase in diameter after treatment and two showed a mild (<5%) decrease, findings were considered to be within normal day-to-day variability (Cornell *et al*. 2004). Finally, the cTnI was rechecked in all patients and remained above the reference range in only one. In this individual, the level had increased from 0.59 ng/L before treatment to 2.47 ng/L. This patient was one of the three in which FS had been normal and was abnormal (<24%) on follow-up. Fig. 2 summarises the changes of CRP, cTnI, fibrinogen, echocardiographic changes and clinical signs.

## DISCUSSION

This study revealed that a high proportion of dogs with SRMA presented concurrent cardiac abnormalities (decreased FS, increased normalised left-ventricular-internal-dimension-at end-systole, spontaneous echocontrast, pericardial effusion and increased cTnI). Although the spontaneous echocontrast, pericardial effusion and increased cTnI often completely resolved in the study dogs following immunosuppressive therapy, the decreased FS and increased normalised left-ventricular-internal-dimension-at end-systole did not always return to normal values and in some cases deteriorated further. The mean age and breeds of the animals in this study were relatively typical of those affected with SRMA, and boxers and beagles were overrepresented as in previous studies (Harcourt 1978, Poncelet & Balligand 1993, Lowrie *et al*. 2009b).

The most common abnormality (12 of 14 cases) identified on echocardiography was of spontaneous echocontrast, which is a characteristic swirling echogenicity of blood in the heart chambers or blood vessels on echocardiography (Bayar *et al*. 2016). It is thought to be due to changes in blood flow or haematological abnormalities. Reported risk factors for spontaneous echocontrast in dogs and humans include increased fibrinogen levels, red cell distribution width, haematocrit, haemoglobin content, hypercoagulability and platelet size and decreased shear rate (Sigel *et al*. 1983, Ralph *et al*. 2011, Bayar *et al*. 2016). Under normal circumstances, red blood cells are repelled from each other because of their similar electrical charge but macromolecules such as fibrinogen alter and reduce these repulsive forces (Fatkin *et al*. 1997).

It has been shown that mean platelet volume is higher in humans with rheumatic mitral stenosis with spontaneous echocontrast, than those without (Bayar *et al*. 2016). Larger platelets are thought to be more active, increasing the potential for red blood cell aggregation, although its clinical relevance is unknown (Balcý *et al*. 2016). In veterinary medicine, it has been shown that dogs with septic peritonitis have larger platelets compared to healthy dogs (Llewellyn *et al*. 2017). On review of the results from this study, 11 of 14 patients had mean platelet volume measured before receiving prednisolone and it was above the normal reference range in three of 11 of these patients (median 11 fL, range 9.2 to 15.8; reference 7.78 to 13.14). No breeds genetically predisposed to having large platelets, such as the cavalier King Charles spaniel, were included in this study and therefore these results may be of significance and warrant further investigation in the future.

Spontaneous echo contrast has been reported previously in three dogs, secondary to systemic inflammatory conditions (including endocarditis, Evan's syndrome and sepsis) resulting in hyperfibrinogenaemia and platelet activation (Ralph *et al*. 2011). Echocardiography was repeated in only one patient, with resolution of the spontaneous echocontrast at 2 weeks but no patients showed signs of cardiac disease. All patients were started on thromboprophylactic therapy but none developed signs of thromboembolic disease.

In our case series we documented that fibrinogen was increased in 11 of 12 cases with SRMA. Fibrinogen is a positive acute phase protein similar to globulin and CRP so it is not surprising that it is increased in dogs with a focal or systemic inflammatory disease such as SRMA. Hyperfibrinogenaemia was not consistently associated with spontaneous echocontrast (cases 4 and 6 had

increased fibrinogen but no spontaneous echocontrast and case 10 had normal fibrinogen but did have spontaneous echocontrast). In addition, the magnitude of the increase in CRP did not seem to be associated with spontaneous echocontrast. This indicates that other factors apart from hyperfibrinogenaemia and increased CRP must be involved in the spontaneous echocontrast that occurs in some dogs with SRMA. This could include changes in blood flow, haemotaocrit, haemoglobin concentration, mean platelet volume or platelet activity and should be further assessed using routine haematology, blood pressure measurement, heart rate recording and platelet function analysis in the future.

In humans, spontaneous echocontrast has been associated with an increased incidence of thromboembolic disease (Rader *et al*. 2007). Although most studies suggest that platelets do not directly cause spontaneous echocontrast but, instead, are activated due to increased red blood cell aggregation or pro-inflammatory states (Fatkin *et al*. 1997), antiplatelet therapy may still be beneficial in the initial management of patients with SRMA. This could be of clinical importance, given that complications due to vascular thrombosis have been reported in SRMA (Spitzbarth *et al*. 2012). Conversely, haemorrhage has been reported in dogs with SRMA and therefore both pro- and antithrombotic states must be considered and investigated further (Hughes *et al*. 2015, Brocal *et al*. 2017).

In this small case series, no antiplatelet or antithrombotic treatments were prescribed and no obvious thrombotic complications occurred. Previous work (de la Fuente *et al*. 2012) documented that dogs with SRMA have increased fibrinolytic activity in their CSF as documented by increased CSF D-dimer concentration. D-dimers are specific markers of fibrinolysis and it would be useful to further examine markers of thrombosis (using D-dimers and fibrinogen degradation products) in dogs with SRMA. Assessment of coagulation using thromboelastography or a platelet function analyser could also assist in determining other factors involved in spontaneous echocontrast in cases of canine SRMA. This could help determine whether antithrombotic or antiplatelet therapy is warranted and whether it is effective.

Cardiac troponin I was measured as an adjunctive method of assessing for cardiac myocyte injury, which could occur as a consequence of myocarditis or secondary to an ischaemic injury. Cardiac troponin I was increased in all patients at baseline and normalised with treatment in all but one. Although cTnI remained increased in that patient, spontaneous echocontrast had resolved. This dog had concurrent mild subaortic stenosis with mild aortic regurgitation. The increased troponin of 2.47 ng/L is consistent with acute myocardial injury and therefore primary cardiac disease other than subaortic stenosis (such as a thromboembolic episode with ischaemic injury) must be considered in this case. In a previous report of a patient with increased cTnI and spontaneous echocontrast (Navarro-Cubas *et al*. 2011), the troponin normalised within 2 weeks of treatment, despite being markedly increased at 16.6 ng/L. Therefore, further work is required to determine the extent and timing of cTnI increase that occurs with inflammatory conditions.

A recent case series (Covey & Connolly 2018) documented cardiac changes in seven dogs with systemic inflammatory diseases, including five with SRMA. All dogs had mild pericardial effusion (not requiring pericardiocentesis) and all had increased cTnI, but none had spontaneous echocontrast. Interestingly, five of seven of these patients had evidence of left venricular systolic dysfunction (decreased FS) on initial echocardiography, including four of five with SRMA. Repeat echocardiography was performed between 4 and 6 days in four patients and at 24 days in one patient. Although pericardial effusion resolved in all dogs, left ventricular systolic dysfunction persisted in three of four dogs with repeat echocardiography. These findings are similar to our present case series, in which five of 14 patients had reduced FS at presentation; only two dogs showed improvement with treatment, while three had persistent left ventricular systolic dysfunction and two additional patients developed reduced FS on repeat echocardiography. Neither the present study nor Covey & Connolly (2018) assessed positive inotropic therapy in these patients. Further investigation into systolic function in patients with systemic inflammation is required to determine whether systolic dysfunction is a negative prognostic indicator and whether positive inotropic therapy is indicated in the short and long term. The finding of persistent or new systolic dysfunction noted in some cases following treatment for SRMA is interesting and warrants further investigation.

In the Covey & Connolly (2018) study, two other patients with inflammatory disease and pericardial effusion were described: one with pleural effusion and one with systemic inflammatory response syndrome (SIRS) of unknown aetiology. SRMA histologically causes fibrinoid arteritis which has been reported to affect the coronary vessels as well as meningeal vessels, resulting in altered vascular permeability that could potentially cause pericardial effusion (Tipold & Schatzberg 2010). However, the pericardial effusion noted in the two cases discussed by Covey & Connolly (2018) which did not have SRMA suggests a secondary mechanism for the development of pericardial effusion, the most likely of which being inflammatory cytokine induced dysfunction in vascular permeability (Snyder *et al*. 1995).

Multiple aetiologies have also been proposed to explain left ventricular systolic dysfunction in patients with systemic inflammatory diseases. Inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 (IL-1) have been associated with SIRS-induced myocardial dysfunction in both humans (Ungureanu-Longrois *et al*. 1995, Stein *et al*. 1996) and dogs (Butler *et al*. 2008). Other mechanisms leading to poor contractility include hypotension, hypoxia and lactic acidosis (Nelson & Thompson 2006). This reduction in myocardial function is generally reversible in humans, with echocardiographic changes resolving within 7 to 10 days after the episode of septic shock (Bulmer 2011). This was not always seen in this case series or in those reported by Covey & Connolly (2018). Although all patients in this study recovered clinically with anti-inflammatory or immunosuppressive therapy, development of myocardial dysfunction has been shown to be a negative prognostic indicator in patients with sepsis and SIRS (Nelson & Thompson 2006). Therefore, positive inotropic drugs such as pimobendan may be indicated in patients with inflammatory conditions and poor systolic function.

Only two of five dogs with pericardial effusion had increased cTnI and it is suspected from this small case series that the effusion and myocyte damage are different cardiac manifestations of systemic inflammation. There was no relationship between the CRP or fibrinogen levels and pericardial effusion, suggesting that effusion has a multifactorial origin and further investigation is required. Although all patients had an increase in CRP and the majority had increased fibrinogen when measured, the cTnI was not consistently increased. As CRP and fibrinogen are markers of inflammation and cTnI is a marker of myocyte damage, they provide different information. Further work is required to investigate why some dogs with systemic inflammation are subject to myocyte damage and pericardial effusion and others are not.

Limitations of this study include the small sample size and the lack of a control group of dogs containing spontaneous echocontrast, pericardial effusion or increased cTnI, but without the diagnosis of SRMA. Examination of systolic function was not a specific aim of this study and therefore more extensive echocardiography was not performed, and assessment of left ventricular systolic function was limited to FS and normalised left-ventricular-internal-dimension-at end-systole. In addition, fibrinogen was not measured in all patients before treatment and was only measured in a small number of dogs after treatment. The three dogs without complete resolution of spontaneous echocontrast and the one dog which showed an increase in cTnI after treatment did not have any further follow-up echocardiography or cTnI measurement, respectively. This lack of long-term follow-up echocardiography is another limitation of our study. Cardiac assessment was incomplete as blood pressure was not measured or heart rate recorded in any of the dogs. Although echocardiography was performed before sedation, anaesthesia or corticosteroid therapy at our hospital, one patient was sedated with medetomidine before referral. Spontaneous echocontrast has been reported to be associated with bradycardia in dogs, in particular those that receive medetomidine (Kellihan *et al*. 2015). This patient had spontaneous echocontrast and increased fibrinogen but did not have an increase in cTnI or reduced FS. In this patient, alpha-2 agonist administration could have contributed to the observed spontaneous echocontrast. Future studies are needed to more thoroughly assess systolic function in dogs with inflammatory conditions.

In conclusion, this study shows that cardiac abnormalities are common in patients with SRMA. Resolution of some of these changes (including spontaneous echocontrast and pericardial effusion) follow immunosuppressive therapy but left ventricular systolic dysfunction can persist in some cases. These findings are similar to those found in humans with inflammatory conditions including CNS disease. The presence of cardiac abnormalities could not be predicted based on the CRP or fibrinogen levels. Further studies are required to determine the cause of these changes and to assess whether or not anti-thrombotic medications or positive inotropic therapy should be considered in the management of canine patients with SRMA.

## Conflict of interest

No conflicts of interest have been declared.

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