**Summary**

Objectives: Despite recognising strokes more commonly in dogs, knowledge regarding long-term outcome and prognostic factors is still sparse. The aims of this study were to describe the incidence of elevations of cardiac troponin I (cTnI) in dogs with acute ischaemic strokes, to evaluate its prognostic value in these patients as well as to characterise the relationship between possible cTnI elevations in dogs with ischaemic strokes and potential underlying cardiac dysfunction.

Materials and Methods: Prospective study of 18 dogs with acute ischaemic stroke diagnosed by magnetic resonance imaging (MRI) of the brain. Serum cTnI concentration, trans-thoracic echocardiography (TTE) and six-lead electrocardiography (ECG) were performed and the findings where available were compared between dogs with good and poor outcome.

Results: cTnI was increased in 17 dogs (median 0.95 ng/mL; range 0.146-153). Focal hyperechoic regions of myocardium were visualised on 2 dogs on TTE; we hypothesise that these represent acute infarcts. A significant association was found between the cTnI concentration and creatinine concentration (P=0.016). No difference in cTnI concentrations was detected between dogs that experienced good and poor outcomes (P=0.421). Clinically significant cardiac dysfunction was only identified in 2 dogs.

Clinical significance: cTnI is commonly elevated in patients diagnosed with acute ischaemic stroke. In this small study population, cTnI did not have a prognostic value but larger studies (recruiting a study population of 98 dogs for a power of 0.8 and a 0.05 alpha/critical value) are necessary to investigate these preliminary results further.

Keywords: cerebrovascular disease, stroke, troponin, dog, outcome

**Introduction**

Cerebrovascular disease is a common cause of acute neurological dysfunction in dogs (Bodreau 2018). Although it was for many years considered a rare occurrence in companion animals, the advent of magnetic resonance imaging (MRI) has shown otherwise. It refers to an abnormality of the brain caused by a disturbance in blood supply and its clinical manifestation, termed a cerebrovascular accident or stroke, is broadly divided into ischaemic (resulting from arterial or venous obstruction) or haemorrhagic (resulting from rupture of blood vessels). The term infarction describes the area of necrotic tissue resulting from ischaemia and the subsequent neuronal and glial cell death (Garosi 2010).

Approximately 50% of dogs diagnosed with ischaemic strokes have concurrent underlying diseases and these most commonly include hyperadrenocorticism, chronic kidney disease, hypothyroidism, and systemic hypertension (Garosi *et al.* 2005). The prognosis for recovery from acute stroke mostly depends on the severity of the neurologic deficits, the initial response to supportive care, and the severity of any underlying cause but no prognostic biomarkers have yet been identified (Garosi 2010). In a study of ischaemic stroke in dogs, approximately one quarter of patients died within the first 30 days of the onset of signs, but those that survived that period had a median survival time of 505 days (Gredal *et al.* 2013). No association has been found between the region of the brain involved (telencephalic, thalamic/midbrain, cerebellum) or the type of infarction (territorial – arising from main arteries of the brain or lacunar – arising from small perforating arteries) and outcome (Garosi *et al.* 2005) and recovery within weeks with only supportive care is commonly reported. It has been suggested that dogs with concurrent medical conditions have shorter survival times than those without an identifiable medical condition (Garosi *et al.* 2005) and that those with right-sided brain lesions had a higher risk of mortality (Gredal *et al.* 2013).

Cardiac troponins are biomarkers routinely used for the diagnosis of acute myocardial infarction (AMI) in humans (Beaulieu-Boire *et al.* 2013). In dogs, studies evaluating the usefulness of measurement of troponins in cardiac disease have mostly focused on individual conditions, revealing that increased troponin concentrations occur in both congenital and acquired heart diseases (Langhorn & Willesen 2016). Myocardial injury has also been documented in a large number of noncardiac diseases, most of them involving critically ill patients, and especially those with inflammatory diseases and shock (Langhorn *et al.* 2014, Langhorn & Willesen 2016) and also in patients with conditions affecting the nervous system (Dutton *et al*. 2018, Spence *et al*. 2019). The pathogenesis of myocardial injury in these conditions is unknown but possible causes including hypotension, hypoxaemia, arrhythmias and microthrombosis have been proposed (Langhorn & Willesen 2016). In many of these noncardiac diseases, elevations in troponins have been associated with short-term fatality (Langhorn *et al.* 2014, Langhorn & Willesen 2016) although its value in determining long-term survival is less clear. Several studies trying to better understand the links between cardiac disease and stroke in human patients have identified an increase in cardiac troponin concentrations in up to 34% of patients with acute stroke (Christensen *et al.* 2004). Increased cardiac troponins in patients with acute ischaemic stroke has been associated with higher rates of mortality and disability but has also been identified in patients without an obvious concurrent myocardial injury (Kerr *et al.* 2009).

Despite recognising strokes more commonly in dogs, knowledge regarding long-term outcome and prognostic factors is still sparse. The aims of this study were therefore to describe the incidence of elevations of cardiac troponin I (cTnI) in dogs with acute ischaemic strokes, to evaluate its prognostic value in these patients as well as to characterise the relationship between possible cTnI elevations in dogs with ischaemic strokes and potential underlying cardiac dysfunction. It was hypothesised that some canine patients following ischaemic stroke would show elevations in cTnI and that this would be associated with a worse outcome.

**Materials and methods**

Dogs diagnosed with ischaemic stroke at the Small Animal Teaching Hospital (SATH) of the University of Liverpool were prospectively recruited for participation in this study between November 2014 and August 2018. Ethical approval for this study was granted by the local Ethics Committee - VREC188. Inclusion criteria included (1) recent onset (less than 7 days) of acute, non-progressive signs of neurological dysfunction, (2) MRI findings compatible with acute ischaemic infarction (lesions hyperintense on T2-weighted and fluid-attenuated inversion recovery images, located within a known vascular territory and causing minimal to no mass effect) and (3) written, informed consent for participation in the study.

For participating cases, serum cTnI concentration and trans-thoracic echocardiography (TTE) were performed within 48 hours of presentation. Whenever possible, six-lead electrocardiography (ECG) was also performed. Echocardiography (2D, M-mode, colour flow and spectral Doppler) were carried out by cardiology Diplomates or cardiology residents under direct supervision of a diplomate. A Vivid 7 machine with Echopac analysis package (GE; Buckinghamshire) were used; measurements were made off-line. Standard 2D echo views were obtained following standard guidelines (Thomas *et al.* 1993). The Simpson’s method of discs (Wess *et al.* 2010) was used to determine left ventricular (LV) end-diastolic and end-systolic volumes and the ejection fraction was calculated. Standard LV M-mode images and measurements were obtained (Sahn *et al.* 1978). The LV chamber diameters and wall measurements in systolic and diastole were normalised for body weight by allometric scaling (Cornell *et al.* 2004). The left atrium to aortic ratio was measured from short axis views in diastole (Hansson *et al.* 2002). Spectral Doppler interrogation of each valve was obtained and the velocities measured. If any valvular regurgitation was evident on colour flow Doppler, peak velocity of regurgitant jets were measured (continuous wave Doppler). Concentrations of cTnI were measured within 4h of collection using an in-house Immulite 2000 (Siemens) assay; the laboratory reference range is ≤0.15 ng/mL. Additional diagnostics, performed in order to investigate for possible underlying conditions, were performed in all cases but varied depending on clinician and owner preferences.

Clinical data recorded for each case included: 1) serum cTnI concentration, 2) signalment (breed, age and sex), 3) location of the infarct in the brain, 4) ambulatory status on presentation, 5) identification of other chronic areas of infarction on MRI, 6) time between onset of signs and cTnI measurement, 7) diagnosis of systemic hypertension (mean systolic blood pressure above 170mmHg on 5 repeated measurements), 8) presence of ECG abnormalities where available, 9) serum creatinine concentration and 10) concurrent diseases identified (based on the results of other diagnostic tests performed). Short (discharge from hospital) and long-term follow-up information was obtained. The outcome was obtained through re-examination at the SATH or telephone conversation with the owners. It was defined as good if there was improvement of the clinical signs without permanent neurological deficits or poor if the suspected infarction or concurrent disease resulted in death, lack of improvement or recurrent neurological deficits.

MRI examinations were performed using a 1.5T (Gyroscan ACS-NT, Philips Medical System) or a 1T (Siemens Magnetom) scanner. The following sequences were obtained in all patients: T2-weighted images (T2WI), fluid-attenuated inversion recovery (FLAIR), T2 weighted gradient echo (GE) sequences and pre- and post-contrast (intravenous injection of 0.1mmol/kg of gadopentetate dimeglumine) T1-weighted images (T1WI). Diffusion weighted imaging (DWI) was used when available.

Statistical analysis was performed using the software SPSS 22.0 (SPSS Inc., Chicago, Illinois, USA). Continuous data were tested for normality using the Shapiro Wilk test. Descriptive statistics are reported for continuous variables using mean (standard deviation) for approximately normally distributed variables and median (minimum-maximum) for variables with skewed distributions, and frequencies are reported for categorical variables. The correlation between age, time between onset of signs and cTnI measurement serum and serum creatinine concentration and serum cTnI concentration was evaluated using Spearman’s rank correlation coefficient. Differences in serum cTnI concentration between dogs with a good or a poor outcome were assessed using the Mann-Whitney U-test. Kaplan-Meier survival analysis was performed to estimate median survival time (MST) with 95% confidence intervals (CI). For all analyses *P*<0.05 was considered significant.

**Results**

During the data collection period (from January 2015 to July 2018), 36 dogs were diagnosed with ischaemic strokes. Eighteen dogs were excluded as the described onset of the clinical signs was more than 7 days prior to presentation (14 dogs) or due to lack of consent from the owners for inclusion in the study (4 dogs). Median cTnI concentration measured in 7 of the dogs presenting with clinical signs lasting longer than 7 days as part of their diagnostic investigation was 0.25 ng/mL (range 0.04-0.75).

Eighteen dogs were therefore eligible for inclusion (Table 1). The median age at presentation was 10.5 years (range 2.8 – 13). There were 10 females (8 neutered) and 8 males (all neutered.) Affected breeds included 3 Lhasa Apso, 3 Shih Tzu, 2 crossbreed and one each of the following breeds: American Bulldog, Cavalier King Charles spaniel, Cocker spaniel, Greyhound, German Shepherd dog, Lurcher, Patterdale terrier, Pomeranian, Pug and Weimaraner.

The infarcts were classified as lacunar in 5 cases and territorial in 13 cases. They were located in the vascular territory of the striate arteries (1), caudal perforating arteries (4) and rostral cerebellar arteries (13). Diffusion-weighted imaging was available for review in 14 cases and confirmed restricted diffusion with lesions hyperintense on DWI images and corresponding signal void in the ADC map. In 6 cases, further lesions compatible with chronic infarctions (based on the presence of contrast enhancement and/or DWI characteristics) were also identified on MRI (Figure 1).

Clinical signs varied depending on the location of the infarct but were in most cases compatible with central vestibular disease and 10/18 dogs were non-ambulatory on presentation. On physical examination, left apical systolic murmurs were reported in 8/18 dogs; all grade 2/6, and one dog also had a systolic click. Median duration of the clinical signs before MRI was 1 day (range 1 – 4) and median duration of the clinical signs before cTnI measurement was 3 days (range 1 – 7). The cTnI was increased in 17/18 dogs (94%) with a median serum cTnI concentration of 0.95 ng/mL (range 0.146 - 153). Repeat cTnI measurements were performed in 4 dogs a minimum of 2 weeks later and median serum cTnI concentration at that time was 0.36 ng/mL (range 0.04 – 0.6). On TTE, preclinical myxomatous mitral valve disease (MMVD) was identified in 13/18 dogs, 5 of which did not have an audible murmur (Table 2). Disease was mild in all dogs, without any evidence of remodelling (Stage B1 by the ACVIM classification; Keene *et al.* 2019). Dilated cardiomyopathy (DCM) was diagnosed in 1 dog (case 2; cTnI 3.62 ng/mL) and moderate aortic stenosis in 1 dog (case 5, also concurrent MMVD; 0.164 ng/mL). Only one dog (the DCM patient) had evidence of left atrial dilatation (short axis diastolic LA/Ao ratio >1.6; Hansson *et al*. 2002). Where good quality spectral continuous wave Doppler envelopes of mitral regurgitation (MR) were recorded to allow peak velocity to be measured (n=10), 6 dogs showed MR velocities exceeding 6 m/s (ref. 5-6 m/s). Based on allometric scaling for body weight (Cornell *et al*. 2004) and excluding the DCM case, no other dog had a dilated left ventricle, with M-mode LV internal diameter in diastole normalised for body weight ranging between 1.14 and 1.63 (ref. 1.27 – 1.85). Only one dog had evidence of concentric left ventricular hypertrophy based on allometric scaling (case 6; systolic blood pressure ranged between 150 and 200 mmHg during hospitalisation; the LV freewall indexed for body weight was 0.79 (ref. 0.29 – 0.6; Cornell *et al*. 2004). Excluding the DCM case, systolic function was mildy impaired in 2 dogs with Simpson’s method of discs derived end-systolic volume indices (ESVI) of 43.6 and 47.2 mLs/m2  respectively (cases 6 and 17); the other 15 cases had ESVI ranging between 6.8 and 31.5 mLs/m2, with systolic dysfunction defined as >30 mLs/m2 (Dukes-McEwan et al. 2003). No spontaneous echocontrast or thrombus was identified in any cardiac chamber from any case. However, two dogs (cases 14 and 16) showed focal hyperechoic regions of myocardium; single in one dog, multiple in the other (Figure 2). Another dog (case 1) had a focal thinned area of left ventricular myocardium, near the apex. Four dogs had mild aortic regurgitation, which was high velocity in one dog (5.97 m/s) reflecting diastolic systemic hypertension in this case (case 5 with moderate aortic stenosis (pressure gradient 70 mmHg); systolic blood pressure by the Doppler method on serial measurements ranged between 168 – 210 mmHg; diastolic blood pressure had not been recorded). Six dogs had mild tricuspid regurgitation, which was at increased velocity in one case (3.03 m/s; ref. <2.8 m/s), consistent with mild systolic pulmonary arterial hypertension.

Electrocardiography results were available for 15 cases (Table 2). These showed sinus rhythms for 13/15. However, 2 dogs (cases 10 and 13) had an accelerated idioventricular rhythm, both with stage B1 myxomatous mitral valve disease. No dog had atrial fibrillation. Other ECG abnormalities included tall R waves (>3.0 mV) in 2 dogs and prolongation of the QRS complexes (>0.06 seconds) in 3 dogs. One dog had a left bundle branch block (case 14). Eight / 15 dogs had notched QRS complexes in at least one lead. No dog showed any significant ST segment abnormalities.

Diagnostic investigations undertaken included haematology, serum biochemistry profile and urinalysis in all dogs, thyroid function tests in 16 dogs, adrenal function tests in 14 dogs, coagulation profile in 12 dogs, thoracic and abdominal imaging in 12 dogs and urine culture in 11 dogs. Concurrent medical conditions were identified in 11/18 dogs based on the results of these investigations. These included renal disease and systemic hypertension in 5 cases (including the one case with dilated cardiomyopathy), primary hypertension in 4 cases and hyperadrenocorticism in 2 cases associated with hypertension in 1 case.

Outcome data is summarised in Table 1. Six dogs were considered to have a poor outcome: 1 dogs was euthanased due to the stroke, 3 dogs were euthanased due to the concurrent diseases initially identified (median survival time could not be estimated as less than 50% of cases died) and 2 dogs had recurrent episodes of acute neurological dysfunction 12 and 17 months later. Two dogs were euthanased for unrelated causes 18 and 45 months after diagnosis and one dog was lost to follow-up approximately 2 months after diagnosis. Nine dogs were alive at the end of the study period (median follow-up time 19 months; range 12 – 48) and according to the owners had no residual neurological abnormalities nor had suffered further episodes of acute neurological deficits since discharge.

A moderate correlation was found between the serum cTnI and creatinine concentration (Spearman Rho: 0.557, P=0.016). No correlation was found between age (P=0.890), time between onset of signs and cTnI measurement (P=0.067) and cTnI concentration. There was no difference in serum cTnI concentration (P=0.421) between patients with good and poor outcomes.

**Discussion**

The results from the present study indicate that cTnI elevation is very common in dogs diagnosed with acute ischaemic strokes but was not shown to differ between dogs experiencing good and poor outcomes. Only 3 dogs had evidence of systolic dysfunction and cardiac disease was not thought to be a common underlying cause for ischaemic strokes in dogs.

The two dogs with more significant cardiac disease (DCM and aortic stenosis) had cTnI levels of 3.62 and 0.164 ng/mL respectively. Although there were several cases with concurrent MMVD (13/18; including the one cases with aortic stenosis), mitral regurgitation was not associated with any structural remodelling such as left atrial dilatation (stage B1; Keene *et al.* 2019); elevated cTnI levels have not been reported in early stages of MMVD (Lee *et al*. 2016; Ljungvall *et al*. 2010) and therefore the increased cTnI measurement was considered unlikely to be due to cardiac disease in this population. The authors considered that the concurrent MMVD diagnosed reflected the older age of this population, which mainly included small breed dogs known to be predisposed to this condition.

 Cardiac arrhythmia, most commonly atrial fibrillation (AF), is a major cause of ischaemic stroke in humans. In human patients recently diagnosed with acute ischaemic stroke, elevations in cTnI concentration were strongly correlated with new-onset AF, higher frequency of potential cardiac sources for stroke and a worse prognosis (Beaulieu-Boire *et al.* 2013). In our population, we failed to identify significant underlying cardiac disease or arrhythmias, despite the prospective evaluation of possible concurrent cardiac dysfunction with a six-lead ECG and TTE. This is in agreement with previous studies in dogs, where cardiac disease was not identified as a common underlying cause for ischaemic stroke (Garosi *et al.* 2005, Gredal *et al.* 2013). Thromboembolic complications associated with canine atrial fibrillation have previously been reported although not in association with stroke (Usechak *et al.* 2012).

Two cases had an accelerated idioventricular rhythm on ECG; these cases had among the highest cTnI levels in our series. Diseases affecting the nervous system have previously been associated with cardiac arrhythmias in human patients and this may reflect perturbed autonomic function, especially catecholamine release (Samuels 2007). These changes can result in cardiac histological evidence of coagulation necrosis (also known as contraction band necrosis); this can lead to rapid calcification of these lesions (Samuels 2007). We speculate that these might be what caused the focal hyperechoic lesions we identified in two of our cases. In another case, focal thinning of the left ventricular apical myocardium was evident, which may represent an old myocardial infarct, similar to those described in cats with hypertrophic cardiomyopathy (Cesta *et al.* 2005). Unfortunately, none of these three cases underwent post-mortem examination, so the suspicion of myocardial infarction remains speculative.

There were some changes evident on electrocardiography in some of these cases. One case had a left bundle branch block and eight cases showed notched QRS complexes in at least one lead. Notched QRS complexes reflect an intraventricular conduction disturbance, which may be a consequence of “microscopic intramural infarction”, which can be associated with ageing or with concurrent cardiac disease, especially if in multiple leads (Winter & Bates 2018). Notched QRS complexes may reflect coronary arteriosclerosis, which is common in dogs with myxomatous degenerative valvular disease and may be associated with myocardial ischaemia and fibrosis (Falk *et al.* 2006; 2013) and chronic valvular disease was the most frequent underlying diagnosis associated with notched QRS complexes in a recent study (Winter & Bates 2018). The dogs showing notched QRS complexes included three with no identified underlying cardiac disease on echocardiography, and only one of thes cases (case 7) had systemic hypertension diagnosed. Systemic hypertension results in a pressure load on the left ventricle, which may be associated with secondary fibrosis which may be an explanation for notched QRS complexes. Without histopathological analysis, any association with the notched QRS complexes remains speculative in these cases, and some authors consider notched QRS complexes, especially in the descending R wave to be normal variants in dogs (Santilli et al. 2018) The two dogs with focal hyperechoic regions within the left ventricular myocardium included the one with left bundle branch block and the other only had one ECG lead (aVL) showing notching. Both had stage B1 MMVD. Myocardial infarction is only rarely described in dogs; usually secondary to other systemic diseases and resulting in impaired left ventricular systolic function or regional wall hypokinesis on echocardiography (Driefuys *et al.* 1998). Focal hyperechoic myocardial lesions, as seen in two cases in this series, have not been described in naturally occurring myocardial infarction in dogs, but it is possible that these are more acute infarcts. However, in the absence of post-mortem histopathological examination, it is not possible to be certain what these lesions corresponded to. If these were lesions of ischaemia or necrosis, they may have contributed to the increased cTnI, regardless of the primary disease process, and whether or not they were associated with the stroke.

Recently, the concept of cardiac vulnerability to cerebrogenic stress has been suggested as an explanation for cTnI elevation after ischaemic stroke (Ahn *et al.* 2016). In this study performed in human patients with acute ischaemic stroke, several ECG abnormalities as well as the lesion location and stroke severity were predictors of cTnI elevation. In addition, a synergistic effect on cTnI elevation by the combinations of cardiac and neurological factors was identified suggesting a possible interaction between heart and brain during the acute stage of ischaemic stroke.

Both human patients and dogs with renal disease have been reported to show an increase in circulating cardiac troponins (Langhorn & Willesen 2016, deFilippi & Herzog 2017). It is thought that they most likely reflect cardiovascular pathophysiology rather than impaired renal clearance and that they remain accurate for evaluation of AMI and acute heart failure in human patients, albeit with a mild reduction in accuracy and a possible need to consider higher cut-offs (deFilippi & Herzog 2017). A positive association with serum creatinine concentration was identified in our patients, similarly to previous studies in dogs (Porciello *et al.* 2008, Sharkey *et al.* 2009), including dogs without evidence of renal insufficiency (Dutton *et al.* 2017). Azotaemia (and other severe systemic diseases) has been reported to increase cTnI levels (Porciello *et al.* 2008), independent of systemic hypertension. However, in another study in dogs with stable chronic kidney disease, creatinine was not associated with cTnI level, which remained within reference ranges (Pelander *et al.* 2017). It can be speculated that the positive association between in cTnI and creatinine in the absence of clinical renal disease could be due to subclinical myocardial damage or due to an altered troponin excretion by the renal system (Dutton *et al.* 2017).

The main limitation of this study is related to the small population of patients evaluated. This preliminary data would indicate that in order to detect as significant a difference similar or larger than demonstrated in this study (with a power of 0.8 and a 0.05 alpha/critical value), we would need to recruit a total of 98 dogs. Outcome endpoints were subjective and in some cases only obtained by telephone conversation with the owners and it is possible that mild neurological deficits would still be detected if examination had been undertaken by a neurologist. Ideally, serial troponin measurements would have been obtained to monitor progression of this biomarker over time. Only surplus blood samples from concurrent investigations were used for this study and performing a venipuncture exclusively for cTnI measurement was not included in the ethical permission granted so this was not possible.

In conclusion, cTnI is commonly elevated in patients diagnosed with acute ischaemic stroke. Cardiac disease was not identified as a common underlying cause for ischaemic strokes. In our small study population, cTnI did not have a prognostic value but larger studies are necessary to investigate these preliminary results further.

**Conflict of interest**

No conflicts of interest have been declared.

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Figure 1.

Magnetic resonance (MR) images of the brain of case 14 illustrating presence of chronic infarctions. A) Sagittal plane T2WI showing acute an infarct in the region of the left rostral cerebellar artery. B) Transverse plane T2WI showing chronic areas of infarction in both the right and left caudate nuclei.

Figure 2.

Right parasternal long axis (A; C) and short axis (papillary muscle level) (B, D) views of Case 14 (A,B) and Case 16 (C,D), showing focal hyperechoic regions within the left ventricular free wall (green arrows in A, B, C). In D, the focal hyperechoic region can be seen in the left ventricular freewall, between the papillary muscles. These may represent myocardial ischaemia or calcification.

Ao = aortic arch, LA = left atrium, LV = left ventricle, RV = right ventricle.