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Cardiac troponin I in cats with hypertrophic cardiomyopathy

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The molecular structure of cardiac troponin I (cTnI) is highly conserved across mammalian species and assays developed for its measurement in human patients have been validated in a number of veterinary species. A raised concentration of circulating cTnI is a sensitive and specific marker of cardiac myocyte injury. Raised levels have been documented in a variety of cardiac diseases in both human and veterinary patients. This study compared serum cTnI concentrations between 16 cats diagnosed with hypertrophic cardiomyopathy (HCM) using echocardiography and 18 control cats. The results show that cats with HCM have significantly higher concentration of serum cTnI (median 0.95 ng/ml, range 0.2–4.1 ng/ml) than control cats (median <0.2 ng/ml, range <0.2–0.25 ng/ml) [$P<0.0001$]. Furthermore in cats with cardiomyopathy a weak correlation was found between the thickness of the left ventricular freewall in diastole measured by ultrasound and serum cTnI concentration ($r^2=0.28$; $P=0.036$). These results suggest that measurement of serum cTnI concentration may enable cats with cardiomyopathy to be distinguished from normal cats using the assay described here.

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most commonly diagnosed cardiac disease in cats (Fox et al 1995, Kittleson 1998). It is characterised by a hypertrophied non-dilated left ventricle in the absence of other cardiac or systemic abnormalities capable of producing a similar phenotype (Fox 1999). Typical morphological changes include myocyte hypertrophy and disarray surrounding areas of increased loose connective tissue (Liu et al 1993). The increased wall thickness and fibrosis cause an increase in left ventricular chamber stiffness and a reduction in left ventricular end diastolic volume. This can result in increased left ventricular diastolic pressure and left atrial pressure leading to congestive heart failure. Left atrial pressure can be further increased in cases of hypertrophic obstructive cardiomyopathy (HOCM) where systolic anterior motion of the mitral valve results in mitral insufficiency (Kittleson 1998).

Circulating cardiac troponin I (cTnI) has been demonstrated to be a highly specific and sensitive marker for myocardial cellular damage in many mammalian species. Increased cTnI concentrations have been documented in cats, dogs and rabbits with myocardial cell injury resulting from contusion, in dogs with arrhythmias secondary to gastric dilatation-volvulus, in dogs with experimentally induced myocardial infarction and in a horse with a ruptured left ventricular outflow tract (Bertinchant et al 1999, Cornelisse et al 2000, Cummings and Cummings 1987, Kirbach et al 2000, Ricchiuti et al 1998, Schober et al 1999, Schober et al 2002). The protein is highly conserved across species and assays used to detect human cTnI have been validated in the dog and cat (Cummings and Cummings 1987, Schober et al 1999, Sleeper et al 2001).

Studies in humans have shown that the protein is released within 4–12 h after myocardial necrosis, reaches a peak concentration in 12–48 h and may persist for 8 days following myocardial injury (Goldmann et al 2001). In cats following blunt thoracic trauma serum cTnI levels have been shown to fall from a peak after 60–72 h (Kirbach et al 2000). Circulating cTnI concentration is used to assess the risk of complications in human patients with myocardial ischaemia,

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myocarditis, arrhythmia, critical illness, cardiac contusion and congestive heart failure (Briassoulis et al 2000, Dolara 1998, Falahati et al 1999, Luna et al 2001, Missov et al 1997, Ottani et al 1999, Ver Elst et al 2000).

Cats with HCM frequently develop ventricular and supraventricular rhythm disturbances that are considered a consequence of myocardial infarction (Fox 1999). Indeed myocardial infarction and secondary fibrosis is not uncommon in feline HCM (Fox 1999). It is therefore possible that cTnI may be used to detect ongoing myocyte necrosis and therefore prove to be a useful indicator of myocardial disease including HCM in this species.

The aims of this study were (a) to compare cTnI levels in clinically healthy cats to cats with HCM; and (b) to correlate cTnI levels with the severity of changes seen on echocardiography.

Material and methods

Animals

Cats referred to the cardiology service of the Queen Mother Hospital for Animals, at the Royal Veterinary College for investigation of suspected heart disease over a 12 month period that were diagnosed with either HCM (nine cats) or HOCM (seven cats) using echocardiography were included in this study (Table 1). The affected cats comprised: 10 domestic short hair; three domestic long hair; one Maine coon and one of each British shorthair and Sphinx. All cats underwent a physical examination, echocardiography, radiography, haematology and biochemistry profiles. In addition, one or more of the following tests were performed in some cats: serum total T4 levels (four cats greater than 7 years old), indirect systolic blood pressure analysis (eight cats with mild azotaemia and/or greater than 7 years old) and electrocardiography (two cats with an arrhythmia detected on physical examination). Six of the cats were diagnosed with congestive heart failure at the time of referral. Ten cats had not received any cardiac medication prior to evaluation of serum cTnI. Medication in the remainder was given for no more than 2 weeks prior to referral and included: frusemide alone (two cats), propranolol alone (one cat), Frusemide and benazepril (one cat), aspirin and enalapril (one cat), frusemide, propranolol and digitalis (one cat).

Eighteen healthy cats (11 domestic short hair, four domestic long hair, two Maine coon, and one British blue) were also evaluated for signs of cardiovascular disease and underwent a physical examination, routine haematology and biochemistry analysis and echocardiography. All parameters were found within normal limits and these cats formed the control group (Table 1).

Haematology and biochemistry

Haematology and biochemistry profiles were performed at the RVC (Abbot Cell-dyn 3500CS, Bayer Opera chemistry system) on all healthy and 12 affected cats using in house reference ranges. Blood analysis on the remaining four cats was performed by the referring veterinary surgeons just prior to referral using a variety of external laboratories and in house systems.

Echocardiography

Standard echocardiographic studies (Thomas et al 1993) were performed using an Acuson Sequoia 512 with a 8V5 5.5–8.5 MHz transducer in non-sedated cats in right lateral recumbency. An ECG was simultaneously recorded in all cats except those that were distressed by the placement of ECG electrodes. Oblique views to fully visualise the heart were also employed. The left atrial to aortic diameter ratio (La/Ao) was obtained using two-dimensional echocardiography from the right parasternal short axis heart base view. M mode measurements of thickness of the inter-ventricular septum in diastole (IVSd), left ventricular internal diameter in diastole and systole (LVIDd, LVIDs), and left ventricular freewall in diastole (LWFWd) were made at the level of the chordae tendineae in the short axis view. Where asymmetrical hypertrophy was identified, the maximum thickness of the area of hypertrophy in diastole was measured from the two-dimensional right parasternal long and short axis view. Papillary muscle size was judged subjectively by one investigator (D.J.C.) as normal or enlarged (Kittleson et al 1999). A diagnosis of HCM was made if the ventricular septum and or left ventricular freewall measured at end diastole was greater than 6 mm thick (Fox 1999), supportive criteria included an La/Ao ratio greater than 1:1.5 and subjective enlargement of the papillary muscles (Kittleson et al 1999). In those cats where a systolic murmur had been detected on auscultation a right parasternal long axis view was used to look for systolic anterior motion of the mitral valve. Doppler echocardiography (colour, pulsed

Table 1. Age, sex, weight and tropinin I levels in 16 cats with HCM (of which seven were classified as obstructive) and 18 healthy control cats

	Age (months) (median; minimum– maximum)	Sex (m:f)	Weight (kg) (median; minimum–maximum)	Troponin (ng/ml) (median; minimum–maximum)	LVFWd (median; minimum–maximum)	IVSd (median; minimum–maximum)
HCM	54; 11–108	8:1	4.2; 2.5–5.7	0.91; 0.24–4.1	6.8; 3.8–11.7	6.5; 5.4–9.1
HCM obstructive	45; 18–96	6:1	3.9; 3.3–5.6	1.30; <0.20–1.70	6.6; 5–9.7	6.3; 5.4–9.6
Control	48; 9–144	9:9	4.7; 3.6–6.9	<0.20; <0.20–0.25	4.35; 3.3–5.7	4.35; 2.9–5.8

wave and continuous wave) was used to characterise flow disturbances and identify cases of HOCM and rule out fixed aortic stenosis. HOCM was diagnosed if in addition to left ventricular hypertrophy one or more of the following was seen: the septal mitral valve leaflet was seen to contact the intra-ventricular septum during systole on two-dimensional imaging, turbulence associated with mitral insufficiency and dynamic left ventricular outflow tract obstruction was seen on two-dimensional colour flow Doppler analysis, an increased peak left ventricular outflow velocity with a characteristic scimitar shape was noted on continuous wave Doppler interrogation (Fox 1999). In cats where a murmur had not been detected SAM of the mitral leaflet was not identified using two-dimensional and colour Doppler examination and therefore Doppler analysis of LVOT velocity was not pursued.

Indirect blood pressure analysis

Systolic blood pressure was measured indirectly using a Doppler flow detector (Parks Medical Electronics) with a 9.7 MHz probe as described previously (Grandy et al 1992, Syme et al 2002). The average of five consecutive measurements was calculated once consistent consecutive readings had been obtained. Hypertension was defined as a systolic arterial pressure of greater than 175 mmHg (Syme et al 2002).

Troponin I measurements

Blood from affected and control cats was collected by jugular venepuncture into serum gel tubes centrifuged at 5000 rpm for 120 s and the serum was stored at −70 °C. Serum cTnI levels were measured by a commercially available immunometric assay using an Immulite® Analyser (Diagnostic Procedures Corporation, Los Angeles) within 1 month of blood sampling. Troponin I was detected by chemiluminescence following protein binding onto beads coated with monoclonal anti-troponin I antibody (Cummings and Cummings 1987). To assess intra-assay variability, five randomly selected serum samples of different cTnI levels were analysed five times on 1 day while inter-assay variability was assessed by aliquoting and freezing five samples of different cTnI levels and analysing them on different days after thawing. Linearity was assessed by diluting a pooled serum sample of high cTnI level to a concentration of $\frac{3}{4}$, $\frac{1}{2}$, $\frac{3}{8}$, $\frac{1}{4}$, $\frac{3}{16}$ and $\frac{1}{8}$.

Statistics

All statistical tests were carried out with standard software (SPSS 10.0 Chicago, USA). cTnI concentrations were evaluated for normality by visual examination of histogram plots and found not to be normally distributed. Therefore non-parametric tests (Wilcoxon Signed Ranks Test) were used to compare serum cTnI between the different groups. cTnI values below the detection limit were ascribed the lowest detectable value of the assay (0.2 ng/ml) for statistical tests. Linear regression between cTnI and cardiac ultrasound measurements were calculated (LVIDd, IVSd, LVIDd, LVIDs, La/Ao ratio). Intra- and inter-assay variability was evaluated by calculating the coefficient of variability (CV). A P-value ≤ 0.05 was considered significant. Sensitivity and specificity of cTnI >0.2 ng/ml for the detection of cardiomyopathy was calculated.

Results

Animals

No difference was seen between affected (obstructive and non-obstructive HCM) cats and control cats as to their age and weight. For signalment, sex and weight see Table 1.

Systolic systemic blood pressure was measured in all cats with cardiomyopathy and found to be less than 170 mmHg.

The CV for the intra-assay variability of cTnI was between 1.8 and 5.7% while the CV for the inter-assay variability was between 2.9 and 7.8%. In samples below 2 ng/ml the maximum difference between highest and lowest value of cTnI was less than 0.2 ng/ml. The largest difference in samples above 4 was 0.6 ng/ml. Dilution of cTnI at defined intervals showed a very good linearity ($r^2=0.998$).

Serum cTnI was below the detection limit (<0.2 ng/ml) in all but two control cats, while all but three cats with cardiomyopathy had cTnI in the measurable range (Table 1). As serum cTnI levels were not significantly different ($P=0.52$) between cats with HCM and HOCM, their data was combined for further analysis. There was a significant difference in cTnI levels between cats with cardiomyopathy and healthy control cats ($P<0.0001$). Sensitivity and specificity of cTnI >0.2 ng/ml for detection of cardiomyopathy was 87 and 84%, respectively.

While a weak correlation between cTnI and LVFWd in cats with cardiomyopathy was found

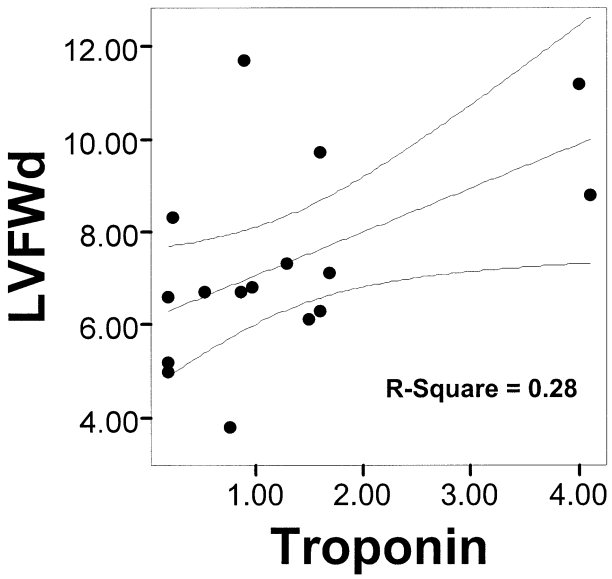

Fig 1. Correlation with 95% CI between serum troponin and LVFWd in 16 cats with hypertrophic cardiomyopathy.

(r^2=0.28; P=0.036) (Fig 1), there was no correlation between cTnI and IVSd (P=0.38), La/Ao ratio (P=0.13), LVIDd (P=0.83) and LVIDs (P=0.46).

In cats with cardiomyopathy, there was no difference in cTnI between those with congestive heart failure (n=6) and those without congestive heart failure (n=10) (P=0.16).

Discussion

The results of this study show that measurement of serum cTnI concentration can distinguish cats with echocardiographic changes consistent with HCM from healthy control cats with a degree of sensitivity and specificity that may prove clinically useful. The results also suggest that 0.2 ng/ml, which is the lowest detectable value of the assay, may be a clinically relevant cut off point to distinguish affected cats from cats without cardiac disease when using this assay.

In this present study two control cats without detectable signs of cardiac or other disease had serum cTnI levels above 0.2 ng/ml (0.21 and 0.25 ng/ml) and this reflects the findings of a previous study where out of 44 Maine coon cats with normal echocardiographic findings two had serum cTnI levels greater than 0.2 ng/ml (0.3 and 0.32 ng/ml) (Connolly personal communications). These results may be due to occult myocardial or arrhythmogenic disease, cross reactivity of the troponin I antibody with another protein in the serum, decrease in the rate of degradation of troponin I in these cats or they may represent normal cTnI levels in clinically normal animals. Indeed in human patients the extent of serum cTnI degradation appears to be highly variable and this variability contributes in part to problems with the standardisation of the assay (Laurino 2000).

In contrast three cats with echocardiographic finding consistent with HOCM had cTnI levels <0.2 ng/ml. Two of the cats were 19 and 20 months of age, respectively, and it is possible that the echocardiographic findings represent congenital mitral dysplasia with associated mitral insufficiency rather than acquired HOCM. It can be difficult to distinguish between these two diseases on ultrasound since both can result in thickening of the left ventricular wall, dilation of the left atrium, mitral insufficiency and dynamic obstruction of the left ventricular outflow tract (Kittleson 1998). It is also possible that myocardial ischaemia and necrosis in HCM is episodic leading to periods where serum cTnI concentrations are normal.

Results of the present study are similar to those of a recent study comparing plasma cTnI levels in 20 cats with HCM from 33 control cats (Herndon et al 2002). The assays used in both studies were different; the present study measured cTnI in serum yielding a reference range in 18 healthy control cats of <0.2–0.25 ng/ml. Our results resemble those of a recent study where measurement of serum cTnI in 28 normal cats showed all values to be below the detectible limit of the assay at 0.5 ng/ml (Kirbach et al 2000). By contrast the study by Herndon et al (2002) measured cTnI in plasma and reported a reference range for cTnI in heparinised plasma in 33 healthy control cats of <0.03–0.16 ng/ml. This reference range reflects that of Sleeper et al (2001) where measurement of heparin plasma levels of cTnI in 21 cats without signs of heart disease on physical examination yielded a reference range between <0.03 and 0.16 ng/ml. The higher value in this present study reflects both the different analyser employed and the use of non-heparinised blood samples. Various assays have been developed for the measurement of cTnI in human patients, which has resulted in a lack of standardisation with up to 10-fold variations, that has been reported in concentrations of cTnI (Goldmann et al 2001). This has led to a wide range of therapeutic cut off points distinguishing normal from abnormal (Adams et al 1993, Goldmann et al 2001).

Heparinised plasma has also been shown to yield lower assay results (Gerhardt et al 2000). A

Table 2. Comparison of results from the present study and the previous study by Herndon et al (2002)

	Present study	Previous study
Correlation	Serum [cTnI]	Plasma [cTnI]
LVFWd	+ve	+ve
IVSd	−ve	−ve
La/Ao ratio	−ve	−ve
LVIDd	−ve	NR
LVIDs	−ve	NR
Presence of CHF	−ve	+ve

The presence of a statistically significant correlation is shown by the +ve symbol. NR, not reported.

comparison of cTnI levels in either plasma or serum taken from the same human patient has shown a significantly lower value by up to 30% in plasma (mean reduction of about 15%) regardless of the analysis method used. This difference may result from the binding of heparin to troponins thereby decreasing their immunoreactivity (Gerhardt et al 2000).

Herndon et al (2002) reported a sensitivity and specificity of 95 and 97%, respectively, for differentiating normal cats from those with moderate to severe HCM. Possible explanations for the lower sensitivity and specificity values in this present report would include: inclusion of possible mitral dysplasia cases into the affected group as outlined earlier, a direct effect of the different assays used or the effect of measuring cTnI in serum compared to plasma and inclusion of less severely affected cats into this present study. Three of the cats with cardiomyopathy only had mild changes on echocardiography with abnormal left ventricular wall thickness ranging from 6.1 to 6.7 mm (serum cTnI levels ranged from <0.2 to 1.5 ng/ml) whereas cat with moderate to severe HCM were entered into the previous study (Herndon et al 2002). Furthermore only 16% of the control cats underwent echocardiographic evaluation in the Herndon study and so it is possible that this group included cats with echocardiographic changes consistent with HCM but not displaying clinical signs. This may result in the inclusion of false negative cats in the control group which would affect the sensitivity and specificity of the test. A comparison of the finding in both studies is shown in Table 2.

Coronary vessel remodelling consisting of thickened arteriolar wall and reduced lumen diameter has been documented in human patients with HCM. This results in reduced coronary blood flow, the severity of which is related to the degree of coronary microcirculation remodelling and myocardial hypertrophy (Schwartzkopff et al 1998). Reduction in subendocardial coronary arteriolar density also reduces coronary vessel capacity and predisposes to myocardial ischaemia (Krams et al 1998, Schwartzkopff et al 1998). Coronary vascular remodelling has also been documented in cats with HCM (Liu et al 1993). If the pathophysiology of the feline disease is similar then it is possible that this remodelling results in myocardial hypoxia and ischaemia causing myocyte death and subsequent cTnI release. It is also possible that the degree of ischaemia would relate to the severity of wall thickening and may explain the correlation between LVFWd thickness and circulating cTnI concentration documented in this present study and that of Herndon et al. (2002). Neurohormonal activation may also induce further myocyte damage and increased levels circulating cTnI as a result of renal sodium and water retention and also by the cardiac remodelling effects of hormones such as angiotensin II, aldosterone and endothelin (Colucci and Braunwald 2001, Krum 2000, Weber 2001). It would be interesting to compare circulating neurohormonal concentrations with cTnI levels in this disease in a future study.

A number of limitations are evident in this study. Although serum cTnI levels were not significantly different between cats with HOCM and HCM it is possible that too few cats were analysed to enable a significant difference to be detected. Equally it is feasible that the presence of SAM of the mitral valve and subsequent dynamic left ventricular outflow tract obstruction does not result in significantly greater myocyte damage and cTnI release. Further investigations using a greater number of affected animals would be needed for a definite conclusion to be reached. The effects of medication following diagnosis (14/16 cats), which consisted of one or more of aspirin, frusemide, spironolactone, atenolol, propranolol, diltiazem, benazapril or enalapril on cTnI concentration, was not further analysed. It would have been useful to measure cTnI concentrations before and after medication, however, the referral nature of the caseload did not make this possible in a useful number of cases. Medication had been administered to five cats for less than 1 week prior to cTnI analysis and aspirin and enalapril had been given for 10 days in one cat (see Materials and methods). It is unlikely that administration of ACE inhibitors and beta blockers for such a short period of time would

have sufficient effect on myocardial remodelling and diastolic function to significantly affect cTnI levels if the $T_{1/2}$ of the protein in cats is similar to that in humans. Frusemide had been given to four cats prior to referral and all had mild azotaemia on presentation to the RVC. It is not possible to fully evaluate the influence of diuretic induced volume depletion on left atrial size and ventricular wall thickness but the cats did not appear clinically dehydrated and their haematocrit and total serum protein levels were within the reference range. Renal insufficiency may have contributed to the azotaemia in some cases. Studies in human patients with renal dysfunction suggest that no significant effect on cTnI levels were seen (Ellis et al 2001). HCM is frequently a progressive dynamic disease and determination of a single serum cTnI concentration gives an indication of myocyte damage at the time of sampling. In this study cTnI was measured at different times in the disease process in the different cats. Although a weak correlation was seen between LVFWd thickness and cTnI concentration it is likely that cats with significant elevations in cTnI concentration but only marginally thick ventricles may have suffered a micro-infarct prior to sampling. To some extend this variable would have been masked if the $T_{1/2}$ of the circulating cTnI is similar in cats to humans since a degree of accumulation of the protein during the disease process would be expected.

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