Journal of Feline Medicine and Surgery (2005) **7**, 289–300
doi:10.1016/j.jfms.2005.01.002

ELSEVIER

jfms

Serum troponin I levels in hyperthyroid cats before and after treatment with radioactive iodine

David J Connolly Bsc, BVetMed, PhD, CertSAM, CertVC, DipECVIM-CA (cardiology)[1*], **Javier Guitian** DVM, PhD, DipECVPH[1], **Adrian Boswood** MA, VetMB, DVC, DipECVIM-CA (cardiology)[1], **Reto Neiger** DrMedVet, PhD, DipACVIM, DipECVIM-CA[2]

[1]*Department of Veterinary Clinical Science, The Royal Veterinary College, Hawkshead Lane, North Mymms Hatfield, Herts AL9 7TA, UK*
[2]*Klinik für Kleintiere, Giessen, Germany*

A raised concentration of serum cardiac troponin I (cTnI) is a sensitive marker of cardiac myocyte injury in the cat and assays developed for its measurement in human patients have been validated in the cat. Raised levels have been associated with a number of cardiac insults including hypertrophic cardiomyopathy and trauma. Hyperthyroidism is a common disease of older cats and excess thyroid hormone is known to produce significant cardiovascular effects in this species. This study evaluated the effect of treatment for hyperthyroidism with radioactive iodine on cTnI concentration, assessed the association between thyroxin levels and glomerular filtration rate (GFR) and cTnI concentration in cats treated for hyperthyroidism and described changes in echocardiographic parameters following treatment. Prior to the treatment serum cTnI was measured and echocardiography performed, thyroxin, cTnI, and echocardiography were then repeated at various time points following radioisotope therapy. The results show that higher thyroxin levels were significantly ($P = 0.002$) associated with a higher likelihood of the cat presenting with detectable levels of cTnI. No significant association was found between GFR and presence of detectable levels of cTnI. Furthermore the results indicate that the effects of hyperthyroidism on echocardiographic parameters appear considerably less in this study than in previous studies and that the main outcome of treatment on these parameters is a significant reduction in fractional shortening ($P = 0.006$). These results suggest that chronic exposure to excess thyroid hormone may induce myocyte damage of sufficient severity to raise serum cTnI concentration in a proportion of cats that resolves following establishment of a euthyroid state.

Date accepted: 25 January 2005

Circulating cTnI has been demonstrated to be a highly specific and sensitive marker for myocardial cellular damage in many mammalian species (Adams et al 1993, Goldmann et al 2001, 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 at 12–48 h and may persist for 8 days following myocardial injury (Goldmann et al 2001). 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 and in dogs with experimentally induced myocardial infarction (Cummings and Cummings 1987, Ricchiuti et al 1998, Bertinchant et al 1999, Schober et al 1999, Cornelisse et al 2000, Kirbach et al 2000, 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). 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). Two studies have also shown significant elevations in cTnI in cats with echocardiographic evidence of hypertrophic cardiomyopathy (Herndon et al 2002, Connolly et al 2003).

*Corresponding author. E-mail: dconnolly@rvc.ac.uk

1098-612X/05/050289+12 $30.00/0

Excess thyroid hormone causes tachycardia and a widened pulse pressure (Klein and Ojamaa 2001). The changes in heart rate result from both an increase in sympathetic tone and a decrease in parasympathetic tone. Cardiac output is increased in the hyperthyroid state due to the combined effects of a decrease in systemic vascular resistance and an increase in resting heart rate, increases in left ventricular contraction and ejection fraction and an increased blood volume (Klein and Ojamaa 2001). The decrease in systemic vascular resistance is a direct result of the vasodilating effect of tri-iodothyronine (T_3) on vascular smooth muscle (Park et al 1997). This results in reduced systemic blood pressure that stimulates the rennin–angiotensin aldosterone system leading to an increase in plasma volume (Resnick and Laragh 1982). Increased T_3 levels can also influence tri-iodothyronine-responsive genes that encode both structural and regulatory protein in the heart such as X and Y myosin heavy chains, sarcoplasmic reticulum Ca^{2+} ATPase, phospholamban, β_1 adrenergic receptor and adenylyl cyclase (Morkin 1993, Ojamaa et al 2000a,b). The increased contractile function of the heart in the presence of raised T_3 levels is a result of the positive and negative regulation of these genes by raised plasma levels of thyroid hormone. The effect of excess T_3 on the cardiovascular system is, therefore, to induce a high output state. The normal heart is capable of compensating for chronically increased cardiac output by cardiac dilation and hypertrophy (Fox et al 1999a).

Clinical cardiovascular manifestations of hyperthyroidism include tachyarrhythmia, cardiac remodelling, increased myocardial oxygen demand and occasionally high output heart failure (Klein and Ojamaa 2001). The influence of hyperthyroidism on cardiac troponin I levels has not been studied in the cat despite the clinical, hormonal and molecular effects of raised T_3 on cardiac function outlined above.

The influence of T_3 on glomerular filtration rate and renal function is well documented in the cat (Adams et al 1997a,b, Becker et al 2000). The effect of altered glomerular filtration rate (GFR) on serum cardiac troponin concentration has been studied in human patient with renal insufficiency. It is generally agreed that serum cardiac troponin concentrations (especially cTnT) are increased in patients with reduced GFR and end stage renal disease. While the cause of this increase is most likely uraemic cardiomyopathy, the influence of reduced renal excretion of cTnI remains controversial (Martin et al 1998, McLaurin et al 1998, Waynard et al 2000, Ellis et al 2001, Lang et al 2001, Freda et al 2002, Ziebig et al 2003). The effect of changes in GFR on cTnI concentration has not been reported in the cat.

The aims of this study were (a) to describe the change in cTnI concentration following treatment with radioactive iodine and its relationship with thyroxin levels and GFR (b) to evaluate changes (if present) in echocardiographic findings following treatment with $Iodine^{131}$.

Materials and methods

Animals

Twenty-three cats referred to the Queen Mother Hospital for Animals at the Royal Veterinary College for investigation and treatment of hyperthyroidism using radioactive iodine were included in this study. All the cats had a history of tachycardia and weight loss, additional finding included polyphagia (18 cats), polydipsia (two cats), diarrhoea (five cats) and aggression (four cats).

All cats underwent a physical examination, haematology and biochemistry profiles, serum total T_4 concentration, indirect systolic blood pressure analysis and urine specific gravity analysis on initial presentation and at 1 month after treatment. In 14 and 19 cats the above tests were repeated 3 months and 6 months after treatment, respectively. The cats did not receive medical management for hyperthyroidism for 4 weeks prior to radioactive iodine therapy. Nineteen cats had been treated medically for hyperthyroidism for a period of 1 month or less before the 4-week washout period and $Iodine^{131}$ treatment. Three cats had received no medical management prior to $Iodine^{131}$ treatment and one cat had received 6 weeks of medical management. In three cats, including the one treated medically for 6 weeks, a euthyroid state was never achieved. Thyroidectomy (bilateral in one case) had been previously performed in four cats.

Three doses of radioactive iodine (111 MBq, 148 MBq or 185 MBq) were given (Amersham Health ICSM London). The dose was determined using the following factors: serum T_4 concentration, severity of clinical signs and thyroid nodule size. The protocol used is shown in Table 1 and represents a modification of the protocol used by Peterson (Peterson and Becker 1995). Radioactive iodine was administered by subcutaneous injection in the sedated animal.

Table 1. Protocol used to determine I^{131} dose for individual cats

Individual scores	Clinical signs	Individual scores	T_4 level (nmol/l)	Total score	Dosage (MBq)
1	Mild	1	<125	<3	111
2	Moderate	2	<125–250	4	148
3	Severe	3	>250	5–6	185

Thyroxin

Serum thyroxin was measured using a competitive chemiluminescent enzyme immunoassay (Immulite (product number 642333); Diagnostic Products Corporation, Los Angeles) and the normal reference range was 19–65 nmol/l. The intra-assay coefficient of variation ranged from 6.3 to 8.4% over a concentration range of 3.8–13 μg/dl. The interassay coefficient of variation ranged from 6.7 to 9.8% over a concentration range of 3.9–13.3 μg/dl. The linearity of the assay was demonstrated up to a dilution of 1 in 8 over a range of physiologically relevant concentrations.

Echocardiography

Standard echocardiographic studies (Thomas et al 1993) were performed in all cats at initial assessment and in 16 cats 6 months after radioactive iodine treatment 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 visualize the heart were also employed to ensure that no areas of asymmetrical hypertrophy were overlooked. 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 interventricular 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. A diagnosis of left ventricular concentric hypertrophy was made if the ventricular septum and or left ventricular freewall measured at end diastole was greater than 6 mm thick by either M-mode or two-dimensional echocardiography (Fox 1999). Fractional shortening (FS) was calculated from the M-mode measurements of LVIDd and LVIDs. 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 wave and continuous wave) was used to characterise flow disturbances including dynamic right ventricular outflow tract obstruction and dynamic left ventricular outflow tract obstruction with associated mitral insufficiency.

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 (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 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 cardiac troponin I levels were measured by a commercially available immunometric assay using an Immulite Analyser (Diagnostic Products Corporation, Los Angeles). The within run and total coefficient of variation described by the manufacturer ranged from 2.7 to 5.8% and 6.1 to 8.4%, respectively, over a concentration range of 0.8–86 ng/ml. The linearity of the assay was demonstrated up to a dilution of 1 in 8 over a range of physiologically relevant concentrations. To assess intra-assay variability in a feline population, five randomly selected serum samples of different cTnI levels were analysed five times on one day while interassay 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 ¾, ½, 3/8, ¼, 3/16, and 1/8. A cTnI value of ≥ 0.2 ng/ml was considered abnormal as described previously (Connolly et al 2003).

Glomerular filtration rate

Glomerular filtration rate was measured on the first, second and forth visit in 15 out of 20 cats and on the first and second visit in five cats. Glomerular filtration rate was not measured in three cats as each owner's consent was not obtained. The procedure was performed by single-injection inulin clearance as previously described (Haller et al 2003).

Briefly, after overnight fasting 3000 mg/m^2 body surface area inulin (Sinistrin; Laevosan, Linz, Austria) was injected intravenously over 30 s. Blood was then drawn from an indwelling catheter after 3, 10, 20, 40, 80, 120 and 180 min and serum inulin measured (Alomed; Rudolfzell, Germany) in a two-step procedure. Finally, inulin clearance and thus glomerular filtration rate was calculated with a two-compartment model. The reference range in healthy cats is 2.07–3.69 (median 2.72) ml/min/kg (Haller et al 2003).

Data analysis

Descriptive statistics were obtained for the concentrations of cTnI and T_4, GFR, blood pressure, heart rate and the echocardiographic findings at each visit. For any visit, less than half of the cats presented with detectable serum concentrations of cTnI. Therefore, it was decided to categorise cats into two groups: with or without detectable serum concentration of cTnI. Levels of cTnI were studied as a binary variable for all subsequent analysis.

The hypotheses that median T_4 concentration, blood pressure, heart rate and the different echocardiographic measurements were different between cats with and without detectable levels of cTnI before the start of the treatment were tested by the Mann–Whitney *U* test of association. The hypothesis that the proportion of cats with detectable levels of cTnI was different before and after treatment was assessed by means of the McNemar test of association.

The relationship between T_4 concentration and GFR and the presence of detectable levels of troponin (>0.2 ng/ml) was assessed with a random effects logistic model. In the model, time following start of treatment was included as a categorical variable with the categories: Initial presentation, 1, 3 and 6 months after treatment. Colinearity between the explanatory variables was assessed by use of correlation coefficients. Models were compared, starting with the full model, with simpler models nested within them by use of the likelihood ratio test. Variables were removed when *P* (LR test) ≥ 0.1 to obtain the most parsimonious model. The reliability of the estimates was assessed checking the sensitivity of the quadrature approximation and the results of the final model were compared to those obtained using generalised estimating equations and a logistic model with robust standard errors (Curtis et al 1993, Dohoo et al 2003).

The values of the different echocardiographic findings before and 6 months after treatment with radioactive iodine were compared using the Wilcoxon signed rank test of association. The same procedure was used to compare blood pressure and heart rate values before and after treatment.

The analyses were carried out using version 7.0 of the statistical package Stata (Stata Corporation, College Station, TX) and SPSS 12 for windows (SPSS Inc., Chicago, IL).

Results

Twenty-three cats were included in the study and comprised of 20 domestic shorthair, two domestic longhair and one Somali. They were between 6 and 15 years old (mean (±SD): 11.4 (±2.6) years) with a mean (±SD) T_4 level before therapy of 166.2 (±86.4) nmol/l. Ten cats received 111 MBq, nine cats 148 MBq and four cats 185 MBq radioactive iodine. Thyroxin levels dropped below or into the normal range 6 months after radioactive iodine in 16 out of 17 cats that were reassessed.

Mean (±SD) of GFR values were 4.029 (±1.459) ml/min/kg for the first visit, 2.488 (±1.002) ml/min/kg for the second visit and 2.642 (±1.070) ml/min/kg for the fourth visit.

The CV for the intra-assay variability of cTnI was between 1.8 and 5.7% while the CV for the interassay 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 ng/ml was 0.6 ng/ml. Dilution of cTnI at defined intervals showed a very good linearity ($r^2 = 0.998$).

Over all the study period, median cTnI concentration for cats with detectable levels was 0.43 (interquartile range: 0.33–0.69; Fig 1).

Before therapy 11 cats had detectable levels of cTnI and in 12 cats cTnI was not detected. After treatment (visit 4) only three of 18 cats presented with detectable concentrations of cTnI. The proportion of cats with detectable cTnI did not significantly differ at the 5% level between the

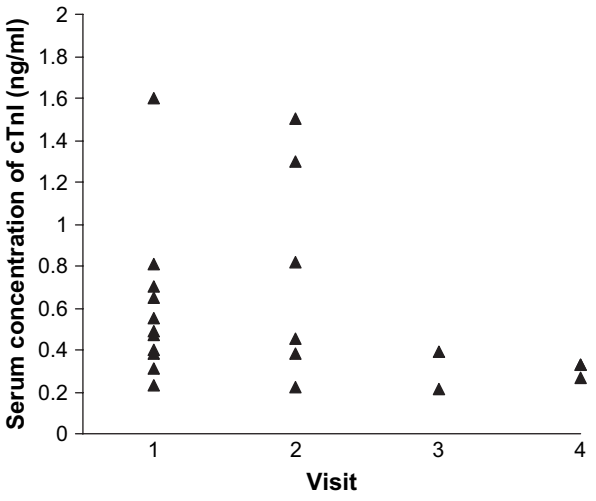

Fig 1. Concentration of serum cardiac troponin I (cTnI) over time for cats with detectable levels (>0.2 ng/ml).

two visits ($P = 0.125$ by McNemar's test). When the actual values were considered the differences were marginally significant ($P = 0.059$ by Wilcoxon signed rank test).

Cats with detectable cTnI before therapy presented with higher T_4 concentration, lower blood pressure and slightly lower heart rate, than cats without detectable levels of cTnI. The differences were not, however, significant at the 5% level. Descriptive statistics for parameters compared before treatment between cats with and without detectable levels or cTnI and the results of the Mann–Whitney *U* test of association are presented in Table 2. Significant differences were found between both groups of cats for two of the echocardiographic findings: median IVSd values in cats with and without detectable cTnI were, respectively, 0.56 cm and 0.46 cm ($P = 0.003$); median IVSs values in cats with and without detectable cTnI were 0.79 cm and 0.7 cm ($P = 0.043$).

During the study period, and mainly in the 2 months following treatment, there was a reduction in the concentrations of cTnI. Eleven out of 23 cats (47.8%) presented with detectable levels at the first visit and in only three out of 18 (16.7%) was cTnI detected in the last visit (Table 3).

The only variable that was retained in the final model for the association between serum concentration of T_4, time after start of the treatment and GFR and presence of detectable levels of cTnI was T_4: higher T_4 levels were significantly ($P = 0.002$) associated with a higher likelihood of the cat presenting with detectable levels of cTnI.

In 10 out of 23 cats a systolic murmur was detected on the initial physical examination before treatment. The murmurs were variable in intensity varying from grade I–III/VI and dependent on heart rate. In five out of 10 cats the murmur was caused by dynamic left ventricular outflow tract obstruction, in three cats the murmur was caused by dynamic right ventricular outflow tract obstruction and in two cats the source of the murmur could not be determined. Six months following treatment a murmur was still present in four out of the 10 cats originally presenting with a murmur. This was due to dynamic right ventricular outflow tract obstruction in one cat, and to dynamic left ventricular outflow tract obstruction in two cats and not determined in one cat. A murmur was detected 6 months following treatment in a single cat that did not have a murmur auscultated before treatment. The cause of this intermittent murmur was not determined. No correlation was seen between the presence of a murmur and serum cTnI levels in this study.

A gallop rhythm was detected in four out of 23 cats on the initial physical examination before radioactive iodine treatment and was still evident in one cat 6 months following treatment.

Descriptive statistics for parameters compared before and after treatment and the results of the Wilcoxon signed rank test are presented in Table 4. Following treatment, there was a significant reduction in heart rate ($P = 0.011$) and the echocardiographic findings IVSs ($P = 0.047$) and fractional shortening ($P = 0.0006$). Marginally significant decrease in LVIDd ($P = 0.056$) was also observed.

Discussion

Almost 50% of hyperthyroid cats have cTnI concentrations within the detectable level of the assay. Interestingly those cats with raised serum cTnI concentration had higher T_4 levels than those cats with undetectable serum cTnI. This difference did not, however, reach significance ($P = 0.12$). The effects of thyroid hormone on the cardiovascular system are well documented and it is likely that higher thyroxin levels would result in increased myocardial oxygen demand caused by increased systolic and diastolic performance, increased cardiac output and reduced systemic vascular resistance (Klein and Ojamaa 2001). Indeed, in this study a significant reduction in heart rate and fractional shortening were identified following normalisation of T_4 levels and a lower indirect blood pressure was found in those cats with detectable cTnI even

Table 2. Echocardiographic findings, blood pressure, heart rate and T_4 concentration in cats with and without detectable levels of cTnI before treatment

Variable		cTnI		*P* (by Mann–Whitney *U*)
		≤0.2	>0.2	
Ao/La	*N*	12	10	0.722
	Percentiles			
	25	0.712	0.593	
	50	0.755	0.801	
	75	0.916	0.933	
LVIDd	*N*	12	10	0.159
	Percentiles			
	25	1.568	1.350	
	50	1.625	1.470	
	75	1.718	1.705	
LVIDs	*N*	12	10	0.923
	Percentiles			
	25	0.615	0.593	
	50	0.695	0.690	
	75	0.860	0.823	
IVSd	*N*	12	10	0.003
	Percentiles			
	25	0.405	0.503	
	50	0.455	0.560	
	75	0.495	0.620	
IVSs	*N*	12	10	0.043
	Percentiles			
	25	0.605	0.640	
	50	0.695	0.785	
	75	0.730	0.890	
LVFWd	*N*	12	10	0.381
	Percentiles			
	25	0.463	0.456	
	50	0.480	0.515	
	75	0.555	0.635	
LVFWs	*N*	12	10	0.582
	Percentiles			
	25	0.703	0.695	
	50	0.740	0.810	
	75	0.875	0.918	
FS	*N*	12	10	0.418
	Percentiles			
	25	48.75	47.13	
	50	55.00	53.00	
	75	61.75	57.25	
Blood pressure	*N*	11	9	0.061
	Percentiles			
	25	180	167.5	
	50	190	171	
	75	215	180	
Heart rate	*N*	11	9	0.370
	Percentiles			
	25	192	161	

Table 2 (*continued*)

Variable		cTnI		*P* (by Mann–Whitney *U*)
		≤0.2	>0.2	
	50	216	210	
	75	250	222	
T_4	*N*	12	11	0.169
	Percentiles			
	25	99.5	107	
	50	124.0	208	
	75	163.5	271	

Ao/La = aortic diameter and left atrial diameter ratio, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, IVSd = thickness of the interventricular septum in diastole, IVSs = thickness of the interventricular septum in systole, LVFWd = left ventricular freewall in diastole, LVFWs = left ventricular freewall in systole.

though the value fell just short of being significant ($P = 0.06$). Results of a recent study have shown that only nine out of 100 hyperthyroid cats were found to be hypertensive which would suggest that systemic vascular resistance decreases in the presence of increased cardiac output in this species (Syme and Elliot 2003). Cardiac troponin I is a sensitive but non-specific marker of myocardial cellular damage (Goldmann et al 2001, Sleeper et al 2001). Detectable levels may, therefore, be expected in a systemic disease which increases myocardial oxygen demand thereby predisposing the myocardium to cellular hypoxia, induces up regulation of angiotensin II and aldosterone resulting in cardiac remodeling and fibrosis. In this study only about 50% of the hyperthyroid cats had detectable cTnI and factors that determine the serum cTnI level include the chronicity of the disease before treatment, the magnitude of the hormonal excess, the degree of remodeling and up regulation of neurohormonal mechanisms such as the rennin–angiotensin aldosterone system and sympathetic nervous system.

A significant difference was seen in hyperthyroid cats with detectable compared to non-detectable cTnI for two of the M-mode echocardiographic measurement: IVSd and IVSs with a thicker IVS present in those cats with detectable cTnI values. Though this may suggest that a greater degree of myocardial remodeling occurred in those cat with detectable cTnI compared to the other hyperthyroid group, care must be taken not to over interpret the importance of a difference of about 1 mm between these M-mode measurements in the two groups. This is especially true as in all the cats with detectable cTnI the IVS thickness was within the normal reference range for this species (Fox 1999). Furthermore, it would be difficult to explain how the multiple biological effects of raised thyroid hormone would result in a phenotype only affecting the IVS and not other parts of the myocardium. In three cats with detectable cTnI and four cats without detectable cTnI a focal area of the IVS distal to the LVOT with a mild increase in thickness that in all cases was less than 6 mm was observed. This was considered an age related change rather than representing true pathology although recently diastolic impairment of focal IVS hypertrophy in a similar position has been described (Simpson et al 2003). As this focal area of hypertrophy was present in both groups of cats it is unlikely that this factor was the cause of the difference in IVS thickness between the two groups. However, the possibility that this area of hypertrophy was included in the M-mode measurement of IVS thickness more frequently in the cats with detectable cTnI cannot be completely eliminated.

Table 3. Cats presenting with detectable levels of troponin at the different visits

Mean number of days following visit 1		*N*	Troponin > 0.2 ng/ml: *N* (%)
Visit 1	–	23	11 (47.8%)
Visit 2	27	23	6 (26.09%)
Visit 3	69	15	2 (13.3%)
Visit 4	91	18	3 (16.7%)

In cats with hypertrophic cardiomyopathy (HCM) arteriosclerosis of intramural coronary arteries is seen (Liu et al 1993, Fox 2003) and the resulting ischaemia and replacement fibrosis has

Table 4. Echocardiographic findings, blood pressure and heart rate before and 6 months after treatment with radioactive iodine

Variable		Visit number		*P* (by Wilcoxon signed rank test)
		1	4	
ALa	*N*	22	16	0.642
	Percentiles			
	25	0.677	0.756	
	50	0.772	0.791	
	75	0.928	0.855	
LVIDd	*N*	22	16	0.056
	Percentiles			
	25	1.438	1.308	
	50	1.595	1.440	
	75	1.713	1.640	
LVIDs	*N*	22	16	0.127
	Percentiles			
	25	0.618	0.720	
	50	0.690	0.805	
	75	0.820	0.920	
IVSd	*N*	22	16	0.254
	Percentiles			
	25	0.443	0.403	
	50	0.490	0.460	
	75	0.570	0.558	
IVSs	*N*	22	16	0.047
	Percentiles			
	25	0.635	0.538	
	50	0.720	0.640	
	75	0.783	0.728	
LVFWd	*N*	22	16	0.210
	Percentiles			
	25	0.460	0.443	
	50	0.490	0.490	
	75	0.573	0.530	
LVFWs	*N*	22	16	0.073
	Percentiles			
	25	0.700	0.640	
	50	0.755	0.755	
	75	0.868	0.830	
FS	*N*	22	15	0.006
	Percentiles			
	25	48.00	40.00	
	50	54.00	43.00	
	75	58.75	50.00	
Blood pressure	*N*	21	15	0.776
	Percentiles			
	25	170	155	
	50	180	180	
	75	195	210	

Ao/La = aortic diameter and left atrial diameter ratio, LVIDd = left ventricular internal diameter in diastole, LVIDs = left ventricular internal diameter in systole, IVSd = thickness of the interventricular septum in diastole, IVSs = thickness of the interventricular septum in systole, LVFWd = left ventricular freewall in diastole, LVFWs = left ventricular freewall in systole.

been suggested as a possible cause of detectable serum cTnI in these animals (Connolly et al 2003). There are limited studies on the histological changes seen in the myocardium in cases of feline hyperthyroidism. In one report histopathology included interstitial fibrosis, endocardial fibroplasias and myocyte disorganisation. However, significant symmetric hypertrophy of the left ventricle was also documented at post mortem (Liu et al 1984). It is, therefore, difficult to conclude whether the detectable serum cTnI in the 11 cats in this study is a consequence of myocardial cellular damage caused by myocardial intramural coronary ischaemia or cellular damage resulting from direct physiological effects of thyrotoxicosis. It is also important to realise that a single serum cTnI value only gives information about cellular damage at one point in time during a dynamic chronic disease process and that cTnI concentration may vary under the influence of factors such as the degree of neurohormonal stimulation and magnitude of β receptor up regulation. This may explain why out of the 12 cats without detectable levels of cTnI before radioactive iodine treatment, cTnI was subsequently detected in two cats on a later visit.

A reduction in GFR following treatment of hyperthyroid cats has been previously described (Becker et al 2000, Slater et al 2003). GFR was not a confounding factor affecting the correlation between T_4 levels and serum cTnI concentration. This finding has not been reported in this species and may suggest that a reduction in GFR does not significantly affect the level of renal excretion of cTnI in the cat.

There is a marked reduction in the number of cats with detectable cTnI levels following treatment with radioactive iodine. Additionally, it was shown that higher T_4 levels were significantly associated with a higher likelihood of the cat presenting with detectable levels of cTnI. It is, therefore, evident that in those cats where raised T_4 levels resulted in cardiomyocte damage from one or more of the mechanisms outlined above, then removal of this supra-normal stimulus reduced the degree of active cellular damage to a level below the detection limit of this test. This reduction occurred relatively rapidly within 2 months of treatment which may suggest that it is associated with down regulation of rapidly acting neurohormonal mechanisms such as RAAS, β receptor density and cellular calcium handling (a significant reduction in heart rate in treated animals was observed) rather than in longer term factors affecting myocardial remodeling.

A second echocardiographic examination was performed in 16 out of the 23 cats, seven of whom had detectable serum cTnI at the first visit. Fractional shortening was shown to be significantly reduced which probably results from a reduction in the stimulatory effects of excess thyroid hormone on total vascular resistance, myocardial contractility and a reduction in total blood volume. A significant decrease in IVSs was also identified, but in the absence of other evidence of significant anatomical remodelling this finding may represent a statistical anomaly rather than the affect of treatment especially since systolic wall thickness is affected by factors such as altered vascular resistance and sympathetic stimulation. Indeed, the change in fractional shortening and heart rate following treatment documented in this report supports the effect of thyrotoxicosis on adrenergic drive. The lack of obvious echocardiographic evidence of significant structural remodelling 6 months after radioisotope treatment supports the impression that the associated decrease in serum cTnI results from the elimination of the immediate physiological effects of excess thyroid hormone, rather than from rectification of any longer term remodelling effects it may have.

A number of previous studies have evaluated the echocardiographic changes in cats with hyperthyroidism (Moise et al 1986, Moise and Dietze 1986, Bond et al 1988). In these reports hyperthyroid cats had significantly higher values for IVSd and LVFWd compared to normal animals and in a proportion of these cases the values were outside the normal reference range (Fox 1999). However, in two of the reports (Moise et al 1986, Bond et al 1988) it was stated that the mean values for these parameters was not significantly different between affected and normal animals. Significant increases were also seen in indices of contractility and LA/Ao ratio in the hyperthyroid cats in these reports. In this present report although a direct comparison between hyperthyroid cats and age matched controls was not made the only highly significant echocardiographic difference between the cats before and 6 months after treatment was a reduction in contractility measured by FS. The failure to find significant structural cardiac changes in this present report especially with relation to the LA/Ao ratio (an indicator of enlarged LA size and a predictor of heart failure) may indicate that feline hyperthyroidism is being diagnosed earlier and with less severe clinical signs as has been recently suggested (Fox et al 1999b).

The presence of a systolic murmur that tended to increase in intensity with increasing heart rate in 10 out of 23 cats with confirmed hyperthyroidism was shown to be due to dynamic left or right ventricular outflow tract obstruction in the majority of cases. These findings are similar to previous reports describing the influence of systemic disease on myocardial systolic function (Sisson 2001, Rishniw and Thomas 2002).

Following treatment the murmurs resolved in 60% of the cats probably as a result of the reduction in heart rate ($P = 0.011$), and resolution of the high output state induced by excess thyroid hormone (Fox et al 1999a).

Study limitations

One limitation of this study is using M-mode measurements for ventricular wall thickness rather than relying on two-dimensional measurements alone. As mentioned in the discussion inclusion of the focal basal IVS thickening in the M-mode measurement may have contributed to the difference in IVSd thickness between cat with and without detectable cTnI. Also it is possible that variation in cursor placement between echocardiographic examinations may introduce inaccuracies into the result. However, as a thorough two-dimensional examination was also carried out using multiple views and no pathological asymmetrical hypertrophy was identified in any of the cats, it is likely that the values recorded are accurate. Indeed, one conclusion of the paper is that supra-normal levels of thyroid hormone appear to have limited if any effects on echocardiographic measurements of ventricular wall thickness. M-mode was employed to allow a more direct comparison with the previously published data on echocardiographic changes associated with thyrotoxicosis and to enable a more accurate determination of end diastole in the small number of cat that would not tolerate ECG placement (nine out of 37 echocardiographic examinations).

A second potential criticism of this study is that in 17 cats medical management had achieved a euthyroid state for a 1–4 week period of prior to Iodine^{131} treatment. In all cases medical management was discontinued for 1 month before Iodine^{131} administration and the cat had raised T_4 at the onset of treatment. It is possible that this brief euthyroid period may have contributed to the minimal changes seen on echocardiography. However, this scenario would require the action of a very rapid remodelling process. Such rapid remodelling would seem unlikely if the mechanisms involved are similar to those responsible for the athletic heart syndrome (Pelliccia et al 2002). Furthermore, this short euthyroid period is unlikely to have any effect on the cTnI levels at the time of measurement because of the short half-life of the protein.

Some cats were not available for re-evaluation at visits three and four. Three cats only presented at visit one and two. This is a common problem in any prospective study but as 20 out of 23 cats were evaluated at least three times during the study period it is unlikely that this would have a significant effect on the conclusions of the study.

Caution should be taken when interpreting the results of the comparisons between cats with and without detectable levels of cTnI before treatment (Table 2) and between the same cats before and after treatment (Table 4). The relatively small sample size limits the ability of our study to detect, as significant differences, changes that might be of biological relevance.

References

Adams JE, Bodor GS, Davila-Roman VC, Delmez JA, Apple FS, Ladenson JH, Jaffe AS (1993) Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation* **88**, 101–106.

Adams WH, Daniel GB, Legendre AM (1997a) Investigation of the effects of hyperthyroidism on renal function in the cat. *Canadian Journal of Veterinary Research* **61**, 53–56.

Adams WH, Daniel GB, Legendre AM, Gompf RE, Grove CA (1997b) Changes in renal function in cats following treatment of hyperthyroidism using ^{131}I. *Veterinary Radiology and Ultrasound* **38**, 231–238.

Becker TJ, Graves TK, Kruger JM, Braselton WE, Nachreiner RF (2000) Effects of methimazole on renal function in cats with hyperthyroidism. *Journal of the American Animal Hospital Association* **36**, 215–223.

Bertinchant JP, Robert E, Polge A, de la Coussaye JE, Pignodel C, Aya G, Fabbro-Peray P, Poirey S, Ledermann B, Eledjam JJ, Dauzat M (1999) Release kinetics of cardiac troponin I and cardiac troponin T in effluents from isolated perfused rabbit hearts after graded experimental myocardial contusion. *Journal of Trauma* **47**, 474–480.

Bond BR, Fox PR, Peterson ME, Skavaril RV (1988) Echocardiographic findings in 103 cats with hyperthyroidism. *Journal of the American Veterinary Medical Association* **192**, 1546–1549.

Connolly DJ, Cannata J, Boswood A, Archer J, Groves EA, Neiger R (2003) Cardiac troponin I in cats with hypertrophic cardiomyopathy. *Journal of Feline Medicine and Surgery* **5**, 209–216.

Cornelisse CJ, Schott 2nd HC, Olivier NB, Mullaney TP, Koller A, Wilson DV, Derksen FJ (2000) Concentration of cardiac troponin I in a horse with a ruptured aortic regurgitation jet lesion and ventricular tachycardia.

Journal of the American Veterinary Medical Association **217**, 231–235.

Cummings B, Cummings P (1987) Cardiac specific troponin-I release in canine experimental myocardial infarction: development of a sensitive enzyme linked immunoassay. *Journal of Molecular and Cellular Cardiology* **19**, 999–1010.

Curtis CR, Kristula M, Galligan DT (1993) Modelling group-level data, individual-level data that are grouped, and repeated dichotomous outcomes using a family of random-effects logistic regression models. *Preventive Veterinary Medicine* **16**, 71.

Dohoo I, Martin W, Stryhn H (2003) Veterinary epidemiologic research. Atlantic Veterinary College Inc., University of Prince Edward Island Charlottetown.

Ellis K, Dreisbach AW, Lertora JL (2001) Plasma elimination of cardiac troponin I in end-stage renal disease. *Southern Medical Journal* **94**, 993–996.

Fox PR (2003) Hypertrophic cardiomyopathy. Clinical and pathologic correlates. *Journal of Veterinary Cardiology* **5**, 39–45.

Fox PR, Broussard JD, Peterson ME (1999a) Hyperthyroidism and other high output states. In: Fox PR, Sissons D, Moise NS (eds), *Textbook of canine and feline cardiology principles and clinical practice* (2nd edn). Philadelphia: WB Saunders, pp. 781–793.

Fox PR, Peterson ME, Broussard JD (1999b) Electrocardiographic and radiographic changes in cats with hyperthyroidism: comparison of populations evaluated during 1992–1993 vs. 1979–1982. *Journal of the American Animal Hospital Association* **35**, 27–31.

Fox PR (1999) Feline cardiomyopathies. In: Fox PR, Sissons D, Moise NS (eds), *Textbook of canine and feline cardiology principles and clinical practice* (2nd edn). Philadelphia: WB Saunders, pp. 621–678.

Freda BJ, Tang WHW, Van Lente F, Peacock WF, Francis GS (2002) Cardiac troponins in renal insufficiency. Review and clinical implications. *Journal of the American College of Cardiology* **40**, 2065–2071.

Goldmann BU, Christenson RH, Hamm CW, Meinertz T, Ohman EM (2001) Implications of troponin testing in clinical medicine. *Current Controlled Trials in Cardiovascular Medicine* **2**, 75–84.

Haller M, Rohner K, Müller W, Reutter F, Binder H, Estelberger W, Arnold P (2003) Single-injection inulin clearence for routine measurement of glomerular filtration rate in cats. *Journal of Feline Medicine and Surgery* **5**, 175–181.

Herndon WE, Kittleson MD, Sanderson K, Drobatz KJ, Clifford CA, Gelzer A, Summerfield NJ, Linde A, Sleeper MM (2002) Cardiac troponin I in feline hypertrophic cardiomyopathy. *Journal of Veterinary Internal Medicine* **16**, 558–564.

Kirbach B, Schober K, Oechtering G, Aupperie H (2000) Diagnostik von herzmuskelschäden bei katzen mit stumpfen thoraxtraumen über biochemische parameter im blut. *Tierärztliche Praxis* **28**, 25–33.

Klein I, Ojamaa K (2001) Thyroid hormone and the cardiovascular system. *New England Journal of Medicine* **344**, 501–509.

Lang K, Schindler S, Forberger C, Stein G, Figulla HR (2001) Cardiac troponins have no prognostic value for acute and chronic cardiac events in asymptomatic patients with end-stage renal failure. *Clinical Nephrology* **56**, 44–51.

Liu SK, Roberts WC, Maron BJ (1993) Comparison of morphologic findings in spontaneously occurring hypertrophic cardiomyopathy in humans, cats and dogs. *American Journal of Cardiology* **72**, 944–951.

Liu SK, Peterson ME, Fox PR (1984) Hypertrophic cardiomyopathy and hyperthyroidism in the cat. *Journal of the American Veterinary Medical Association* **185**, 52–57.

Martin GS, Becker BN, Schulman G (1998) Cardiac troponin I accurately predicts myocardial injury in renal failure. *Nephrology Dialysis Transplant* **13**, 1709–1712.

McLaurin MD, Apple FS, Falahati A, Murakami MM, Miller EA, Sharkey SW (1998) Cardiac troponin I and creatine kinase-mb mass to rule out myocardial injury in hospitalised patients with renal insufficiency. *American Journal of Cardiology* **82**, 973–975.

Moise NS, Dietze AE, Mezza LE, Strickland D, Erb HN, Edwards J (1986) Echocardiography, electrocardiography, and radiography of cats with dilation cardiomyopathy, hypertrophic cardiomyopathy and hyperthyroidism. *American Journal of Veterinary Research* **47**, 1476–1486.

Moise NS, Dietze AE (1986) Echocardiographic, electrocardiographic, and radiographic detection of cardiomegaly in hyperthyroid cats. *American Journal of Veterinary Research* **47**, 1487–1494.

Morkin E (1993) Regulation of myosin heavy chain genes in the heart. *Circulation* **87**, 1451–1460.

Ojamaa K, Kenessey A, Klein I (2000a) Thyroid regulation of phospholamban phosphorylation in the rat heart. *Endocrinology* **141**, 2139–2144.

Ojamaa K, Klein I, Sabet A, Steinberg SF (2000b) Changes in adenylyl cyclase isoforms as a mechanism for thyroid hormone modulation of cardiac β adrenergic receptor responsiveness. *Metabolism* **49**, 275–279.

Park KW, Dai HB, Ojamaa K, Lowenstein E, Klein I, Sellke FW (1997) The direct vasomotor effect of thyroid hormones on rat skeletal muscle resistance arteries. *Anaesthesia and Analgesia* **85**, 734–738.

Pelliccia A, Maron DJ, De Luca R, Di Paolo FM, Spataro A, Culasso F (2002) Remodeling of left ventricular hypertrophy in elite athletes after long-term deconditioning. *Circulation* **105**, 944–949.

Peterson ME, Becker DV (1995) Radioiodine treatment of 524 cats. *Journal of the American Veterinary Medical Association* **207**, 1422–1428.

Resnick LM, Laragh JH (1982) Plasma renin activity in syndromes of thyroid hormone excess and deficiency. *Life Science* **30**, 585–586.

Ricchiuti V, Sharkey SW, Murakami MM, Voss EM, Apple FS (1998) Cardiac troponin I and T alterationsin dogs hearts with myocardial infarction: correlation with infarct size. *American Journal of Clinical Pathology* **110**, 241–247.

Rishniw M, Thomas WP (2002) Dynamic right ventricular outflow obstruction: a new cause of systolic murmurs in cats. *Journal of Veterinary Internal Medicine* **16**, 547–552.

Schober KE, Cornand C, Kirbach B, Aupperle H, Oechtering G (2002) Serum cardiac troponin I and cardiac troponin T concentrations in dogs with gastric dilation-volvulus. *Journal of the American Veterinary Medicine Association* **221**, 381–388.

Schober K, Kirbach B, Oechtering G (1999) Non-invasive assessment of myocardial cell injury in dogs with suspected cardiac contusion. *European Journal of Veterinary Cardiology* **1**, 17–25.

Simpson KE, French A, Dukes McEwan J, Gunn-Moore D, Koffas H, Moran C, Corcoran BM (2003) Diastolic

impairment in cats with a lone septal bulge. A pulsed Doppler Tissue Imaging Study. *BSAVA Congress 2003 Scientific Abstracts* **100**, 609

Sisson D (2001) Evaluation of cats with suspected heart disease. *BSAVA Congress 2001 Scientific Proceedings* 173–174

Slater LA, Neiger R, Haller M, Mueller W, Stevens KB, Church DB (2003) Long-term changes in glomerular filtration rate in hyperthyroid cats following treatment with iodine^{131} (abstract). *Proceedings of the 13th ECVIM-CA Congress* 154

Sleeper MM, Clifford CA, Laster LL (2001) Cardiac troponin I in the normal dog and cat. *Journal of Veterinary Internal Medicine* **15**, 501–503.

Syme HM, Barber PJ, Markwell PJ, Elliot J (2002) Prevalence of systolic hypertension in cats with chronic renal failure. *Journal of the American Veterinary Medical Association* **220**, 1799–1804.

Syme HM, Elliot J (2003) The prevalence of hypertension in hyperthyroid cats at diagnosis and following treatment (abstract) *Proceedings of the 13th ECVIM-CA Congress* 167

Thomas WP, Gaber CE, Jacobs GJ, Kaplan PM, Lombard CW, Moise NS, Moses BL (1993) Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. Echocardiography Committee of the Speciality of Cardiology, American College of Veterinary Internal Medicine. *Journal of Veterinary Internal Medicine* **4**, 247–252.

Waynard D, Baum H, Schatzle G, Scharf J, Neumeier D (2000) Cardiac troponin T and I in end-stage renal failure. *Clinical Chemistry* **46**, 1345–1350.

Ziebig R, Lun A, Hocher B, Priem F, Altermann C, Asmus G, Kern H, Krause R, Lorenz B, Möbes R, Sinha P (2003) Renal elimination of troponin T and troponin I. *Clinical Chemistry* **49**, 1191–1193.