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REVIEW

## Cardiac biomarkers in cats



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### KEYWORDS

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**Abstract** Cardiac biomarkers have been used in cats as part of the clinical assessment of heart disease for over a decade. They are widely available to practitioners through commercial reference laboratories. The evidence base for the use of cardiac biomarkers (primarily N-terminal pro-B type natriuretic peptide and cardiac troponin I) in cats is comprehensively reviewed in this article, focusing on each of six specific areas: distinguishing cardiac from non-cardiac causes of respiratory distress; measurement of cardiac biomarkers in urine and pleural fluid; identification of occult cardiomyopathy; effects of systemic disease on circulating concentrations of cardiac biomarkers; point-of-care biomarker testing, and the possible prognostic utility of cardiac biomarker measurement.

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### Introduction

For over a decade, the measurement of cardiac biomarkers has been reported in cats with a variety of cardiac and systemic diseases, and measurement of N-terminal pro-B type natriuretic peptide (NTproBNP) and cardiac troponin I (cTnI) has now become commonplace in general and referral practices. The diagnosis of cardiac disease in cats poses particular challenges to many practitioners,

including: a high prevalence of sub-clinical (or 'occult') cardiomyopathy, the inconsistent implications of a heart murmur in asymptomatic cats of different ages, and a tendency for the first clinical signs of heart failure to be of sudden onset and severe. These assays offer a straightforward and accessible test, which often feature in the diagnostic investigation of feline cardiac disease by veterinarians in general and referral practice alike. However, understanding of the clinical utility of these laboratory tests is ever evolving.

This review was aimed at updating the reader on the published veterinary literature regarding

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### Abbreviations

CHF	congestive heart failure
CKD	chronic kidney disease
cTnl	cardiac troponin I
cTnT	cardiac troponin T
HCM	hypertrophic cardiomyopathy
NPV	negative predictive value
NTproBNP	N-terminal pro-B type natriuretic peptide
PPV	positive predictive value

cardiac biomarkers in cats. The physiology of the natriuretic peptides and cardiac troponins has been reviewed in detail elsewhere. The focus of this review was on the role of cardiac biomarkers in clinical decision-making.

### Review methods

Published literature was searched using Medline, Web of Science and Google Scholar electronic databases.<sup>c,d,e</sup> The terms used in various combinations are listed in Table 1. The reference lists of retrieved articles were also manually searched and the relevant citations were retrieved. Conference proceedings and research abstracts were not included as part of the formal review process, but the findings of two recent research abstracts were chosen for report because of their specific relevance to this area of study. Information recorded from each reviewed publication included: citation details; biomarkers measured; the assay used; the number of animals; and the hypothesis, findings, conclusions and limitations of each study. A second party then crosschecked this for errors.

Summaries of the studies reviewed in this manuscript were tabulated (Tables 2–5) for quick reference. This review initially considers biomarkers measured in reference laboratories. Some of the newer, point-of-care tests are considered later in this manuscript.

### Distinguishing cardiac from non-cardiac causes of respiratory distress

Cats with respiratory distress are often unstable and frequently intolerant of any handling or

**Table 1** Search terms used in combination to review electronic online databases for recent published literature on feline cardiac biomarkers.

Biomarker	Natriuretic
Cardiac	NTproANP
Cardiomyopathy	NT-proANP
Cat	NTproBNP
cTnl	NT-proBNP
cTnT	Peptide
Feline	Troponin

diagnostic interventions. Although echocardiography is useful for identifying cats with cardiogenic respiratory distress, it may not always be available. Measurement of a cardiac biomarker may be helpful if a blood sample can be obtained with minimal restraint, and this might be safer than thoracic radiography. Eight studies were identified that compared cardiac biomarker concentrations in cats with cardiac and non-cardiac causes of respiratory distress: four studies investigated cTnl<sup>1–4</sup> and four investigated natriuretic peptides (of which, all four featured NTproBNP and one also featured NTproANP)<sup>5–8</sup> (Table 2).

Of the cTnl studies, 75% reported a higher median cTnl concentration in the cardiac vs. the non-cardiac group and one failed to detect a statistically significant difference. The study in which no difference was detected<sup>1</sup> also had the smallest sample size, so this finding may reflect that the statistical comparison was under powered. All studies in which a difference was identified reported a considerable overlap in cTnl values between cardiac and non-cardiac groups, suggesting that a single cut-off value to identify cardiogenic dyspnea in cats is unlikely to be clinically useful.

In contrast, NTproBNP has shown greater accuracy in distinguishing cats with cardiac dyspnea from those with non-cardiac causes: all four studies reviewed reported higher median NTproBNP concentration in cats with cardiogenic respiratory distress.<sup>5–8</sup> The one study investigating NTproANP reported that the overall accuracy of this test was lower than NTproBNP, but despite this, the test was still useful for detecting cardiogenic dyspnea.<sup>6</sup> Published NTproBNP cut-off values for identifying cats with acute congestive heart failure (CHF) ranged from 214 to 277 pmol/L, with a sensitivity generally over 85% and a specificity of 84–88%. However, because these studies were published over a 5-year time frame and used three different commercially available assays, the cut-off values and sensitivity/specificity data should not be

<sup>c</sup> <http://www.ncbi.nlm.nih.gov/pubmed>.

<sup>d</sup> <http://wok.mimas.ac.uk/>.

<sup>e</sup> <http://scholar.google.com/>.

directly compared. Also, recent changes in commercial assay methodology may mean that established cut-off values are replaced by new publications using contemporary assays. Despite this, the evidence convincingly supports the use of NTproBNP to differentiate between cardiac and

non-cardiac causes of respiratory distress in cats. As discussed below, a significant practical limitation of the published literature is the current lack of studies investigating the utility of a patient-side NTproBNP test, which has only recently become available.

**Table 2** Summary of the studies reporting the use of cardiac biomarkers to differentiate between cardiac and non-cardiac causes of respiratory distress in cats.

Biomarkers	Number of cats	Conclusions	Citation	Evidence category
cTnI	16 cats with HCM, 18 healthy controls	cTnI can help distinguish between HCM and non-HCM groups, but is less able to identify cats with CHF <sup>a</sup>	Connolly <sup>3</sup>	P;C;E
	43 cats with dyspnea (31 cardiac)	Able to identify cardiac causes of dyspnea: AUC 0.84. <sup>b</sup> Overlap between groups	Herndon <sup>4</sup>	P;M;C;E
	53 cats with dyspnea (23 cardiac)	Significant difference between cardiac and non-cardiac: AUC 0.84. <sup>c</sup> Overlap between groups	Connolly <sup>5</sup>	P;M;C
	39 dyspneic cats (25 cardiac) 37 healthy controls	A patient-side cTnI assay can be used to differentiate cats with cardiac causes of dyspnea from those with non-cardiac disease and normal controls <sup>d</sup>	Wells <sup>6</sup>	P;M;C;E
NTproANP NTproBNP	85 dyspneic cats (44 cardiac)	Both NTproANP <sup>e</sup> and NTproBNP <sup>f</sup> were able to discriminate between cardiac and non-cardiac patients, but NTproBNP better performance (cut-off 220 pmol/L, AUC 0.96)	Connolly <sup>8</sup>	P;C;B
NTproBNP	162 dyspneic cats (101 cardiac)	Reliable discrimination between cardiac and respiratory causes of dyspnea: cut-off 207 pmol/L, AUC 0.98 <sup>g</sup>	Fox <sup>7</sup>	P;M;C;E
	21 cats with pleural effusion (11 cardiac disease)	NTproBNP successfully discriminated between cardiogenic and non-cardiac causes of pleural effusion: cut-off 258 pmol/L, AUC 1.0 <sup>g</sup>	Hassdenteufel <sup>9</sup>	P;C;B;E
	40 cats with pleural effusion (22 cardiac)	Plasma NTproBNP reliably identified cats with cardiogenic pleural effusion: cut-off 214 pmol/L, AUC 0.91 <sup>g</sup>	Humm <sup>10</sup>	P;C;E

AUC, area under the curve, pertaining to receiver operating curve statistical analysis of diagnostic test utility; CHF, congestive heart failure; cTnI, cardiac troponin I; HCM, hypertrophic cardiomyopathy; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; P, prospective study design; M, multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E, echocardiography on all cats.

<sup>a</sup> Immulyte (Diagnostic Products Co.).

<sup>b</sup> Stratus (Dade Behring).

<sup>c</sup> Immulyte (Siemens Medical Diagnostics).

<sup>d</sup> i-Stat 1 analyser (Heska Corp.).

<sup>e</sup> proANP 1-98 (Guildhay Ltd).

<sup>f</sup> Cardioscreen NTproBNP (Guildhay Ltd).

<sup>g</sup> CardioPet proBNP (IDEXX Ltd).

## Pleural fluid and urinary NTproBNP measurement

In humans, NTproBNP concentration can be accurately measured in pleural fluid and urine.<sup>9,10</sup> The same has been shown in 40 cats presenting to an emergency department with pleural effusions.<sup>8</sup> In both urine and pleural effusion samples, NTproBNP was detectable with adequate performance. The NTproBNP concentration was significantly higher in pleural fluid than in plasma, with a strong

correlation between measurements, suggesting that measurement of NTproBNP in pleural fluid obtained during therapeutic thoracocentesis is an adequate and reliable substitute for blood sampling, thereby reducing handling of these dyspneic patients. The urine NTproBNP to creatinine ratio was higher in the cats with cardiogenic pleural effusion than in those with non-cardiac causes. Despite this, further analysis failed to determine useful cut-off values to distinguish between cardiac and non-cardiac patients using urinary

**Table 3** Summary of the studies reporting the use of cardiac biomarkers to detect occult heart disease in cats.

Test	Number of cats	Conclusions	Citation	Study design
cTnl	16 cats with HCM, 18 healthy controls	cTnl can help distinguish between HCM and non-HCM groups, but is less able to identify cats with CHF <sup>a</sup>	Connolly <sup>3</sup>	P;C;E
	53 cats: 20 HCM and 33 healthy controls.	cTnl could discriminate between HCM and control cats, and was also correlated with LV wall thickness <sup>b</sup>	Herndon <sup>11</sup>	P;M;B;C
	73 cats: 53 cardiac and 20 healthy controls	cTnl was higher in cats with heart disease than control cats (assay validation study) <sup>c</sup>	Langhorn <sup>20</sup>	P;C;E
NTproANP	36 cats: 17 HCM and 19 healthy controls	No significant difference between HCM and control cats, but a mild positive correlation with LVFW thickness and LA size was detected <sup>d</sup>	Maclean <sup>15</sup>	P;B;C;E
	Study 1—5 cats Study 2—22 cats: 14 cardiomyopathy and 8 controls	Positively correlated with LA pressure. Significant difference between cardiac and control groups <sup>e</sup>	Hori <sup>16</sup>	P;C;E
	43 cats: 16 heart disease/CHF, 16 heart disease/NO-CHF, 11 controls	Positively correlated with LA size. Discriminated between all 3 groups <sup>f</sup>	Zimmering <sup>18</sup>	P;B;C;E
NTproANP NTproBNP	78 cats: 33 heart disease/CHF, 17 heart disease/NO-CHF, 28 controls	Both biomarkers <sup>g,h</sup> distinguished between all 3 groups, and were correlated with each other. NTproBNP <sup>h</sup> was more accurate at detecting cardiac disease: cut-off 49 pmol/L, AUC 0.98. Both markers positively correlated with LA size and E:E' ratio.	Connolly <sup>17</sup>	P;B;C;E
NTproBNP	41 cats: 9 normal, 12 equivocal HCM, 19 moderate/severe HCM. Maine Coon or Maine Coon-cross only	Higher NTproBNP in severe group, no significant difference between all other groups: not an effective screening test in this population. <sup>i</sup> Severe HCM cut-off 44 pmol/L, AUC not reported. MYBPC3:A31P mutation positive cats had higher NTproBNP	Hsu <sup>12</sup>	P;C;E

(continued on next page)

Table 3 (continued)

Test	Number of cats	Conclusions	Citation	Study design
	201 cats: 99 normal, 9 equivocal HCM, 15 mild HCM, 17 moderate HCM, 61 severe HCM	No difference in NTproBNP between equivocal and healthy cats. <sup>h</sup> Severe HCM had significantly higher NTproBNP than other groups. Cut-off for mild HCM detection 100 pmol/L, AUC 0.96	Wess <sup>13</sup>	P;C;B;E
	227 cats: 114 normal, 87 HCM, 22 UCM, 3 UCM, 1 DCM	NTproBNP effectively discriminated between normal cats and those with occult cardiomyopathy. <sup>j</sup> Cut-off 99 pmol/L, AUC 0.92. Correlation of NTproBNP with LV wall thickness and LA size.	Fox <sup>14</sup>	P;M;C;B;E
	146 cats: 43 normal, 16 equivocal, 50 mild heart disease, 37 moderate/severe	NTproBNP SNAP test can be used to help exclude moderate to severe occult cardiomyopathy; negative predictive value 94% <sup>k</sup>	Machen <sup>19</sup>	P;M;C;B;E

AUC, area under the curve, pertaining to receiver operating curve statistical analysis of diagnostic test utility; CHF, congestive heart failure; cTnI, cardiac troponin I; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricular; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; NO-CHF, no current or previous congestive heart failure; UCM, unclassified cardiomyopathy; P, prospective study design; M, multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E, echocardiography on all cats.

<sup>a</sup> Immulyte (Diagnostic Products Co.).

<sup>b</sup> Stratus CS troponin I (Dade Behring Inc.).

<sup>c</sup> ADVIA Centaur CP TnI-ultra (Siemens).

<sup>d</sup> proANP 1-98 Biomedica, (American Laboratory Products Co.).

<sup>e</sup> Shinonoria-ANP radioimmunoassay (Shionogi Co.).

<sup>f</sup> proANP 1-98 (Biomedica Group, Immundiagnostik AG).

<sup>g</sup> proANP 1-98 (Guildhay Ltd).

<sup>h</sup> Feline Cardioscreen proBNP (Guildhay Ltd).

<sup>i</sup> Feline Cardiocare NTproBNP (Veterinary Diagnostics Institute).

<sup>j</sup> Cardiopet proBNP (IDEXX Ltd).

<sup>k</sup> NTproBNP SNAP (IDEXX).

NTproBNP; this possibly related to variable handling or processing times for urine samples in the study. Further studies with improved standardization of urine sample collection from cats with suspected cardiac disease are needed.

### Identification of cats with occult cardiomyopathy

Occult heart disease is common in cats and, currently, a veterinary cardiologist screens most cats using echocardiography. However, some cat owners may be reluctant to travel or pay for a cardiologist to perform echocardiography, highlighting a possible role for cardiac biomarkers to pre-screen those cats most likely to benefit from echocardiography. Eleven published studies compared a control group of healthy cats to a group of cats with echocardiographic evidence of heart disease, but no clinical signs of CHF<sup>1,11–19</sup> (Table 3). Of these, only the two largest studies

were specifically designed to test the ability of cardiac biomarkers for identifying occult cardiomyopathy in a screened population of cats. One investigated the use of a quantitative NTproBNP assay,<sup>14</sup> whilst the second evaluated a patient-side SNAP colorimetric assay.<sup>19</sup> In all, the 10 published studies described a total of 393 healthy cats, 350 cats with hypertrophic myopathy (HCM), 38 with restrictive or unclassified cardiomyopathy, five with dilated cardiomyopathy, and one with arrhythmogenic right ventricular cardiomyopathy. Broadly, all but one of these studies reported that cardiac biomarkers were significantly higher in cats with echocardiographic evidence of cardiomyopathy than in cats without cardiac disease.

In three studies, the NTproANP was reported to be significantly higher in cats with echocardiographic evidence of heart disease than healthy controls.<sup>16–18</sup> In contrast, one small study<sup>15</sup> did not detect a significant difference between cats with

**Table 4** Summary of the studies reporting the use of cardiac biomarkers in patients with non-cardiac disease.

Test	Number of cats	Conclusions	Citation	Study design
cTnI	23 hyperthyroid cats (18 post-treatment with RAI)	cTnI higher in cats with higher total thyroxine concentration. Trend towards reduction in cTnI observed, but not statistically significant <sup>a</sup>	Connolly <sup>22</sup>	P;B;E
NTproBNP cTnI	23 hyperthyroid cats (12 post-treatment with RAI), 17 cats with HCM, 19 controls	cTnI was increased in 46% and NTproBNP was increased in 38% hyperthyroid cats with no echocardiographic abnormalities. Both biomarkers normalized in most hyperthyroid cats after RAI treatment <sup>b,c</sup>	Sangster <sup>24</sup>	P;C;B;E
NTproANP NTproBNP	85 hyperthyroid cats at baseline, 61 after treatment with RAI	Hyperthyroidism was associated with a significant but modest elevation of both natriuretic peptides, which reduced after RAI treatment <sup>b</sup> .	Menaut <sup>23</sup>	P;M
cTnI	14 cats with CKD	cTnI higher in azotemic patients, but no correlation with creatinine concentration <sup>c</sup>	Porciello <sup>25</sup>	
NTproANP NTproBNP	58 cats: 22 normal, 13 CKD normotensive, 23 CKD hypertensive	NTproBNP higher in cats with severe azotemia, but no correlation with creatinine. NTproBNP was higher in hypertensive CKD than non-hypertensive CKD. Also correlated with systolic BP and age. NTproBNP reduced after treatment of hypertension. NTproANP similar, but did not reduce after treatment. <sup>d,e</sup>	Lalor <sup>26</sup>	M;C
cTnI	49 cats: 18 anemic, 31 non-anemic, unwell controls	cTnI higher in anemic cats than controls, but no correlation with PCV <sup>f</sup>	Lalor <sup>27</sup>	P;C

AUC, area under the curve, pertaining to receiver operating curve statistical analysis of diagnostic test utility; BP, blood pressure; CHF, congestive heart failure; CKD, chronic kidney disease; cTnI, cardiac troponin I; HCM, hypertrophic cardiomyopathy; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; PCV, packed cell volume; RAI, radioactive iodine treatment; P, prospective study design; M, multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E, echocardiography on all cats.

<sup>a</sup> Immulite (Diagnostic Products Co.).

<sup>b</sup> Cardiopet NTproBNP (IDEXX).

<sup>c</sup> Stratus CS Stat cTnI (Dade Behring).

<sup>d</sup> NTproANP 1-98, (Biomedica Gruppe).

<sup>e</sup> VETSIGN Feline Cardio-SCREEN proBNP, (Guildhay Ltd).

<sup>f</sup> Immulite (Siemens).

and without heart disease, but reported a weak positive correlation between NTproANP and left atrial size.

NTproBNP has been reported to be significantly higher in cats with heart disease than healthy cats in all five studies reporting this comparison. Three studies reported an optimal NTproBNP cut-off value for detecting occult cardiomyopathy: two

studies identified 100 pmol/L (71–92% sensitivity, 94–100% specificity),<sup>13,14</sup> and one identified 49 pmol/L (sensitivity 100%, specificity 89%).<sup>17</sup> The assay used was identical in two of these studies,<sup>13,17</sup> and the echocardiographic measurement used for the diagnosis of cardiomyopathy (diastolic left ventricular wall thickness  $\geq 6$  mm) was identical in all three publications. It should



**Table 5** Summary of the studies reporting prognostic capability of cardiac biomarkers in cats.

Test	Number of cats	Conclusions	Citation	Study design
NTproANP	68 cats: 25 heart disease/CHF, 26 heart disease/NO-CHF, 17 controls	Increased NTproANP was associated with reduced survival time in univariable analysis, but lost significance in multivariable analysis when included with LA size <sup>a</sup>	Zimmering <sup>37</sup>	P;B;C;E
cTnI cTnT	36 cats with HCM (10 cardiac death) 23 healthy controls	cTnI and cTnT were both higher in non-survivors than survivors. cTnI correlated with LVFW thickness at diagnosis <sup>b,c</sup>	Langhorn <sup>38</sup>	P;B;E
NTproBNP cTnI	41 cats with HCM (21 cardiac death)	cTnI provided prognostic information, independent of heart failure status and the presence of left atrial dilation. NTproBNP was significantly associated with prognosis only if heart failure status or LA size was not accounted for <sup>d,e</sup>	Borgeat <sup>39</sup>	P;B;E

AUC, area under the curve, pertaining to receiver operating curve statistical analysis of diagnostic test utility; CHF, congestive heart failure; cTnI, cardiac troponin I; HCM, hypertrophic cardiomyopathy; LA, left atrial; NO-CHF, no current or previous congestive heart failure; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; LVFW, left ventricular free wall; P, prospective study design; M, multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E, echocardiography on all cats.

<sup>a</sup> proANP 1-98 (Biomedica Group, Immundiagnostik AG).

<sup>b</sup> Stratus (Dade Behring).

<sup>c</sup> Elecsys hs-TnT (Roche).

<sup>d</sup> Cardiopet NTproBNP (2nd Gen; IDEXX).

<sup>e</sup> AccuTnI (Beckman Coulter).

be noted that the study reporting a lower optimal NTproBNP cut-off value<sup>17</sup> enrolled a smaller number of control cats and a smaller number of cats with occult heart disease than the other two publications (control groups:  $n = 28$  vs.  $n = 99$  and  $n = 114$ ; occult cardiomyopathy:  $n = 17$ , vs.  $n = 113$  and  $n = 93$ ; see Table 3). Because of this, it is possible that the range of NTproBNP variability in normal cats was underestimated in this publication, leading to a lower diagnostic cut-off for occult cardiomyopathy.

In those studies that tested the ability of NTproBNP to distinguish between different grades of severity of cardiomyopathy,<sup>12–14,19</sup> this biomarker was less accurate at identifying mild grades of disease. This suggests that echocardiography remains preferable for screening mild/early stage disease. In one study, Maine Coons positive for the MYBPC3:A31P mutation had significantly higher NTproBNP than mutation-negative cats.<sup>12</sup>

Both studies comparing cTnI in cats with heart disease (without heart failure) to healthy controls reported that circulating concentrations of this biomarker were significantly higher in cats with

heart disease,<sup>1,11</sup> as did a recent validation study for a high sensitivity cTnI assay.<sup>20</sup> However, with the larger samples sizes reported and the similarities in results between the published studies, NTproBNP currently seems the better cardiac biomarker to use when screening for occult cardiomyopathy.

### Effects of systemic disease

In humans, circulating cardiac biomarker concentrations are known to be influenced by age, sex, renal and thyroid function, body condition (especially obesity), and the presence of anemia.<sup>21</sup> Although the effects of body weight, age and sex have not been well studied in cats, the effects of some non-cardiac diseases have been investigated. Six published studies evaluated the effects of non-cardiac, non-respiratory disease on circulating cardiac biomarkers (Table 4). Three investigated hyperthyroid cats,<sup>22–24</sup> two investigated chronic kidney disease (CKD, plus/minus hypertension),<sup>25,26</sup> and one reported preliminary data in anemic cats.<sup>27</sup> All three studies regarding the effect of hyperthyroidism provided strong

evidence that NTproANP ( $n = 61$ ),<sup>23</sup> NTproBNP ( $n = 84$ ),<sup>23,24</sup> and cTnI ( $n = 46$ )<sup>22,24</sup> are increased in a hyperthyroid state, and return to the same level as non-hyperthyroid controls after restoration of a euthyroid state by radioactive iodine therapy. One of these studies<sup>24</sup> compared hyperthyroid cats with separate control groups of normal cats and a separate group of cats with cardiomyopathy. In this study, both NTproBNP and cTnI were higher in cats with cardiomyopathy than hyperthyroidism, but significant overlaps were present between groups, suggesting that neither biomarker can effectively differentiate between cats with hyperthyroidism and primary cardiomyopathy. The consistent finding that cTnI is increased in hyperthyroid cats suggests that not only are cardiac filling pressures affected by changes in systemic vascular resistance and circulating volume induced by the endocrinopathy, but that thyrotoxicosis affects the myocardium on a cellular level to cause myocardial cell damage (either by a direct effect of thyroid hormones or an indirect effect, for example via sympathetic nervous system activation).

In cats with azotemic CKD, cTnI is often higher than the reference interval for healthy cats. However, one study failed to identify a significant correlation between the severity of azotemia and the degree of cTnI elevation, suggesting that the azotemic state may be more important than the degree of renal functional impairment when comparing individual cats to reference intervals.<sup>25</sup> However, the results of this study merit some additional research, because no control group was used and none of the 14 cats investigated had echocardiography performed.

Natriuretic peptides have also been evaluated in cats with CKD. One study reported the values of NTproANP and NTproBNP in cats with CKD (with and without hypertension) and compared them with a control group of non-hypertensive cats without evidence of CKD.<sup>26</sup> The NTproBNP was significantly higher in cats with severe azotemia ( $>440 \mu\text{mol/L}$  or  $5 \text{ mg/dL}$ ) than those with less severe CKD and healthy controls but, again, no correlation with creatinine concentration was detected. Also, NTproBNP was higher in hypertensive CKD than non-hypertensive cats with CKD, and circulating concentrations reduced after successful treatment of hypertension. Similar to NTproBNP, NTproANP was higher in severely azotemic cats and those with hypertension. However, unlike NTproBNP, NTproANP did correlate with serum creatinine concentration and did not normalize with treatment of systemic hypertension. The reasons for these differences are

unclear, but this and the findings of several other studies suggest that NTproBNP is more sensitive to dynamic changes than NTproANP. As with the cTnI study above,<sup>25</sup> this study of natriuretic peptides in cats with CKD did not include echocardiographic examination of any of the subjects. Also, the control group was not age-matched with the hypertensive and non-hypertensive CKD groups. These limitations mean that further, prospective, standardized studies in cats with CKD  $\pm$  hypertension are warranted, where echocardiography is performed to account for the presence of occult cardiac disease and where a control group is age- and sex-matched to the cats with CKD.

One recent study investigating the effect of anemia on cTnI in cats showed that anemic cats had significantly higher circulating cTnI than a control population of unwell, non-anemic cats.<sup>27</sup> However, this study was subject to similar methodological flaws, in that echocardiography was not performed on all cats and the authors did not report the frequency with which auscultated abnormalities (such as a gallop sound, arrhythmia or murmur) were present in the anemic group. Cats with auscultated abnormalities were, however, excluded from the control group of non-anemic cats.

### Point-of-care tests

Much interest has been expressed in developing patient-side cardiac biomarker assays, primarily for use in cats with respiratory distress, in the hope that this may help practitioners more confidently diagnose and treat acute CHF. Another potential application for these in-clinic tests would be to help primary clinicians stratify cats with heart murmurs, according to which are most likely to have occult cardiomyopathy and therefore require echocardiography. Two studies evaluating patient-side cardiac biomarker tests in cats with cardiac disease have been published,<sup>4,19</sup> with one research abstract being recently presented.<sup>f</sup>

The performance of the first patient-side NTproBNP ELISA (IDEXX Ltd) was tested in a recent study of 146 cats.<sup>19</sup> The ability of this colorimetric test to identify cats with moderate-to-severe heart disease amongst a population of cats referred for cardiac investigation suggested a good

<sup>f</sup> Hezzell M, Rush J, Rozanski E, Cunningham S, Oyama M. Differentiating cardiac vs non-cardiac causes of pleural effusion in cats using plasma and pleural fluid with a point-of-care NTproBNP test. *J Vet Intern Med* 2015 <http://dx.doi.org/10.1111/jvim.12609>.



performance in identifying moderate and severe grades of occult heart disease. The assay had a positive cut-off NTproBNP concentration of between 108 and 122 pmol/L, similar to the cut-off of 100 pmol/L for detection of moderate/severe occult cardiomyopathy previously reported.<sup>14</sup> The negative predictive value (NPV) of the patient-side test was 94% (i.e. in a cat with a negative test result, there was a 94% probability that this patient truly did not have moderate-to-severe heart disease). Although the positive predictive value (PPV) was 64%, this also aids identification of a population of asymptomatic cats where echocardiography is indicated to screen for occult disease. These figures suggest that the patient-side test has significantly greater utility to 'rule-out' more advanced heart disease than it does to confirm the presence of disease. The population described in this study had a high prevalence (24%) of moderate-to-severe heart disease. In a different population of lower prevalence of moderate-to-severe heart disease, such as the background general practice population, the PPV would be even lower (equivocal and mild cardiomyopathy is more common); importantly, however, the NPV of the test would increase. For example, if screening a population of shelter cats for HCM, which has an estimated overall prevalence of 15%,<sup>28</sup> the NTproBNP point-of-care test would have a PPV of 49% and an NPV of 97%, presuming the same test sensitivity and specificity. This would make it a useful test for identifying cats with no or mild disease, for which further diagnostic interventions such as echocardiography are unlikely to add significant additional information to the practitioner. A notable exception to this would be when screening cats used for breeding, where echocardiography would still be required to detect mildly affected cats. Also, the confounding influence of hyperthyroidism to increase circulating NTproBNP concentration should be considered in older cats where point-of-care testing is performed.<sup>23,24</sup>

To date, the ability of this point-of-care NTproBNP test to distinguish between cardiac and non-cardiac causes of respiratory distress has not been reported in a published study. However, one research abstract did report evaluation of this test in a population of cats with pleural effusion owing to both cardiac and non-cardiac diseases. The point-of-care test performed favorably on plasma, but did have a relatively low specificity for cardiac disease (87.5%, 95% CI 64–96.5%).<sup>f</sup> In the same study, the test was also evaluated on pleural fluid NTproBNP (see above) and had a lower specificity on this sample type (64.7%, 95% CI 41.3–82.7%).<sup>f</sup> Despite the questionable clinical

utility of a positive point-of-care NTproBNP test in a cat with pleural effusion, it is reasonable to assume that a negative colorimetric test in a dyspneic cat is likely to reflect a non-cardiac cause of clinical signs. No studies have been published that have investigated the utility of point-of-care tests in dyspneic cats without a pleural effusion.

In contrast, patient-side cTnI analysis has been investigated in 37 cats to identify cats with a cardiac cause of acute respiratory distress.<sup>4</sup> In this study, cTnI was significantly higher in cats with cardiac disease than in those with a respiratory cause of dyspnea. Cats with a circulating cTnI concentration <0.24 ng/mL all had a non-cardiac cause of clinical signs, whereas all cats >0.66 ng/mL had cardiogenic dyspnea. In this population, none of the cats had sepsis, such as pyothorax, as a cause of dyspnea. Sepsis is known to increase circulating cTnI concentrations in humans and dogs<sup>29–31</sup> and the same may be true in cats. If so, the findings of this study may not be applicable to a wider population of cats that includes patients with pyothorax.

### Prognostic utility of cardiac biomarkers

In humans, NTproBNP, cTnI and cTnT have been used to stratify patients with HCM according to prognosis.<sup>32–36</sup> Three studies have been published that investigated the association of cardiac biomarker concentration with outcome in cats with heart disease; one investigated NTproANP,<sup>37</sup> one investigated both cTnI and cTnT,<sup>38</sup> and one investigated NTproBNP and cTnI (Table 5).<sup>39</sup>

In a study evaluating 68 cats with varying degrees of cardiomyopathy severity, NTproANP was the first cardiac biomarker evaluated for an association with survival time in cats with cardiomyopathy.<sup>37</sup> Although significant at the univariable level, NTproANP did not remain significant in multivariable analysis when included alongside echocardiographic measures of left atrial size, suggesting that once left atrial size was known, no additional prognostic information was gained by the measurement of NTproANP. Similarly, in another study of 41 cats,<sup>39</sup> higher NTproBNP was associated with reduced survival time in cats with HCM at the univariable level, but did not remain additionally useful once clinical signs or left atrial size were accounted for.

Cardiac troponins may be more useful than natriuretic peptides in providing prognostic information in cats. The circulating concentration of cTnI and cTnT at diagnosis were significantly higher in cats that suffered cardiac death than survivors in one recent study investigating 36 cats

with HCM.<sup>38</sup> The cTnT was a better prognostic marker in this study, with cTnI showing no additional prognostic utility. The results also suggested that serial biomarker monitoring might be clinically useful, because cTnT measurement repeated before the end of the follow-up period in this cohort of cats provided independent prognostic information, even when accounting for cTnT concentration at the time of diagnosis. A second study, reporting 41 cats with HCM, identified this same association between increased cTnI and a greater risk of cardiac death.<sup>39</sup> Cats with a circulating concentration of cTnI >0.7 ng/mL at the time of diagnosis had a shorter time to cardiac death, independent of both clinical signs of CHF and echocardiographic measures of left atrial size or function. In this study, cats with regional left ventricular hypokinesia detected on echocardiography had significantly higher cTnI than cats without regional hypokinesia, possibly reflecting an association between increased cTnI and regional myocardial ischemia or infarction. It is worth noting that these two studies<sup>38,39</sup> used different cTnI assays, so despite the similar patient demographics and the publication of these two articles within months of one another, the reported cTnI values were not comparable.

Currently, no published studies have thoroughly evaluated how cardiac biomarkers may change over time in cats with cardiomyopathy. One recently presented research abstract<sup>8</sup> suggested that a >70% change in quantitative NTproBNP measurement was required to indicate a genuine change, instead of day-to-day biological or assay variability. In our own clinics, it is advised that an increased NTproBNP test (or positive patient-side SNAP test) be followed up with echocardiography rather than re-testing, so our personal experience with this is limited. In dogs, the rate of change in cardiac biomarker concentration appears important in long-term prognosis, but this has not been reported in cats and it is not understood how this may help to predict outcome in feline patients.

## Limitations

Most of the studies that have been reviewed had a prospective design and the investigative protocol was standardized, where possible. However, treatment protocols were not standardized and

differences in decision-making between different veterinarians and different owners will no doubt have affected survival time in the studies evaluating prognosis.

No consensus exists amongst veterinary cardiologists as to how best to grade severity of cardiomyopathy in cats, other than to say most cats that have experienced clinical signs of CHF have severe disease. In the screening studies reviewed here, where cats with cardiomyopathy were classified into groups of equivocal, mild, moderate and severe by some studies, this lack of consensus means that different authors classified cats in different ways. For example, in some groups, severe cardiomyopathy took into account left atrial size, but in others, it only accounted for degree of wall thickening. As a result, cats classified as 'severe' in some studies may have been classified as 'moderate' in others. This lack of consensus means that the reader cannot directly compare the findings of different screening studies by utilizing cardiac biomarkers. In addition, a lack of consensus and an inconsistency in the echocardiographic measurement technique between veterinary cardiologists means that even the current 'gold-standard' of diagnosing mild (or equivocal) HCM may not be reliably comparable between publications, and this may account for some of the differences in optimal NTproBNP cut-off values reported in different studies.

Misclassification of patients into broad groups is possible, such as presence or absence of cardiac disease, or suffering a cardiac vs. non-cardiac death. An example of this was identified by Humm and colleagues,<sup>8</sup> who reported a suspected misclassification of one cat in their study, despite all patients having been assessed by a veterinary cardiologist using echocardiography. This may have led to falsely low specificity of pleural fluid NTproBNP to detect cardiogenic pleural effusion in their article. Other studies did not perform echocardiography on all cats included, so the presence of cardiac disease in many patients was not assessed, and some studies did not exclude patients with systemic hypertension or hyperthyroidism from their cardiac disease group. Although a heterogeneous population of cats is more likely to be reflective of the wider general practice population, misclassification of cases and the presence of concurrent systemic disease affecting the cardiovascular system are likely to reduce the discriminative ability of the cardiac biomarker tests reported in certain studies. This is especially true in studies with a small sample size or low event rate, such as is the case in many veterinary studies.

<sup>8</sup> Harris A, Estrada A, Gallagher A, Mincey B, Lamb K, Bohannon M, Hanscom J, Mainville C. Biological variability of N-terminal pro-brain natriuretic peptide in adult healthy cats. *J Vet Intern Med* 2015 <http://dx.doi.org/10.1111/jvim.12609>.

Finally, two aspects of laboratory technique are important to consider. The use of different assays in different studies limits the utility of published cut-off values to clinicians comparing their measured biomarker concentration to those reported in the literature. This is especially important to note for cTnl, where five different assays were used across the 13 papers reviewed here. Another limitation is the difference between NTproBNP concentration measured by the 'second-generation' IDEXX Feline Cardiopet NTproBNP assay and the previous assay used by the same laboratory (although the manufacturer states that values are likely to be comparable). It is likely that studies published before 2014 did not use the more sensitive second-generation NTproBNP assay from IDEXX, so cut-off values may not apply to practitioners testing cats at the time of writing, even though they are using the same reference laboratory.

## Summary

The published literature on cardiac biomarkers in cats is widespread, and recent studies have widened the understanding of the emerging roles for cardiac biomarkers in cats with heart disease, especially in relation to the development of the convenient patient-side assay and the use of these biomarkers for long-term prognosis.

The NTproBNP appears to most reliably differentiate between cardiac and non-cardiac causes of respiratory distress in cats. Measurement of NTproBNP from pleural fluid obtained by thoracocentesis is reliable and obviates the need for blood sampling restraint in an unstable patient. The patient-side test will increase the convenience of NTproBNP testing in cats in general practice, and this test has great potential to assist in the emergency room. However, the usefulness of NTproBNP in prognostication is limited where left atrial dilation and a history of CHF can be reliably confirmed. In contrast, measurement of cTnl can be used not only as a patient-side test to differentiate cardiac from non-cardiac causes of respiratory distress (albeit less accurately than NTproBNP), but can also be used as part of prognostication together with heart failure status and echocardiographic measurements.

On the basis of current published data, future studies evaluating urinary NTproBNP:creatinine ratio as a diagnostic test are warranted. The value of the patient-side NTproBNP ELISA in distinguishing between cardiac and respiratory causes of respiratory distress has not yet been published, so its use in the acute patient would currently be

based upon limited data. There is notable overlap between the NTproBNP concentrations reported in cats with respiratory disease and the established cut-off value used for the diagnosis of occult cardiomyopathy by the patient-side test, so the potential for false-positive results when using the point-of-care test in acute patients should be considered, as supported by data recently presented as a research abstract.

The current evidence base for how systemic non-cardiac diseases affect the circulating concentrations of cardiac biomarkers is weak for cats with CKD and systemic hypertension, and further studies are warranted in these patients. However, hyperthyroid cats are relatively well studied and the evidence from which to draw conclusions is more reliable.

In the authors' opinions, practitioners should cautiously interpret absolute cut-off values from the published literature, due to differences in the commercial troponin assays used by different studies, and differences in NTproBNP assay sensitivity at reference laboratories. However, the available results suggest that cardiac biomarkers will continue to have clinical utility for veterinary cardiologists and are likely to have an increasingly important role in both primary and referral veterinary practice.

## Conflicts of Interest

In the last 3 years, the authors have each received discounted biomarker analysis from IDEXX laboratories in the UK for the purposes of research in cats. We wish to confirm that there are no conflicts of interest associated with this publication and there has been no financial support for this work from any third parties or funding bodies.

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