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1 **Cardiac Biomarkers in Cats**

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8

9 Abbreviations

10 NTproBNP, N-terminal pro-B type natriuretic peptide; cTnI, cardiac troponin I; cTnT, cardiac troponin
11 T; HCM, hypertrophic cardiomyopathy; LV, left ventricular

12

13

14 **Introduction**

15 For over a decade, the measurement of cardiac biomarkers has been reported in cats with a variety
16 of cardiac and systemic diseases, and measurement of N-terminal pro-B type natriuretic peptide
17 (NTproBNP) and cardiac troponin I (cTnI) has now become commonplace in general and referral
18 practice. The diagnosis of cardiac disease in cats poses particular challenges to many practitioners,
19 including a high prevalence of sub-clinical (or “occult”) cardiomyopathy, the inconsistent implications
20 of a heart murmur in asymptomatic cats of different ages, and a tendency for the first clinical signs of
21 heart failure to be sudden onset and severe. These assays offer a straightforward and accessible test,
22 which often feature in the diagnostic investigation of feline cardiac disease by vets in general and
23 referral practice alike. However, our understanding of the clinical utility of these laboratory tests is
24 ever evolving.

25 This review aims to update the reader on the published veterinary literature regarding cardiac
26 biomarkers in cats. The physiology of the natriuretic peptides and cardiac troponins is reviewed in
27 detail elsewhere,^{1,2} and the focus of this review will be on the role of cardiac biomarkers in clinical
28 decision-making.

29

30 **Review Methods**

31 Published literature was searched using Medline, Web of Science and Google Scholar electronic
32 databases.^{a,b,c} Terms used in various combinations are listed in Table 1. The reference lists of retrieved
33 articles were also manually searched and relevant citations retrieved. Conference proceedings were
34 not included. Information recorded from each publication included citation details; biomarkers
35 measured; the assay used; the number of animals, and the hypothesis, findings, conclusions and
36 limitations of each study. This was then cross-checked by a second party for errors.

37 A summary of the studies reviewed in this manuscript is tabulated (Tables 2-5) for quick reference.
38 This review initially considers biomarkers measured in reference laboratories. Some of the newer,
39 point-of-care tests are considered later in this manuscript.

40

41 **Distinguishing cardiac from non-cardiac causes of respiratory distress**

42 Cats with respiratory distress are often unstable and tolerate poorly any handling or diagnostic
43 interventions. Although useful to identify cats with cardiogenic respiratory distress, echocardiography
44 may not be available. Measurement of a cardiac biomarker may be useful if a blood sample can be
45 obtained with minimal restraint, and this may be safer than thoracic radiography. Eight studies were
46 identified that compared cardiac biomarker concentrations in cats with cardiac and non-cardiac
47 causes of respiratory distress: 4 studies investigated cTnI³⁻⁶ and 4 investigated natriuretic peptides (of
48 which, all 4 featured NTproBNP and 1 featured NTproANP)⁷⁻¹⁰ (Table 2).

49 Of the cTnI studies, 3/4 reported a higher median cTnI concentration in the cardiac vs. the non-cardiac
50 group and one failed to detect a statistically significant difference. The study where no difference was
51 detected³ also had the smallest sample size, so this finding may reflect that the statistical comparison
52 was under-powered. All studies where a difference was identified reported a considerable overlap in
53 cTnI values between cardiac and non-cardiac groups, suggesting that a single cut-off value to identify
54 cardiogenic dyspnea in cats is unlikely to be clinically useful.

55 In contrast, NTproBNP has shown greater accuracy in distinguishing cats with cardiac dyspnea from
56 those with non-cardiac causes: all 4 studies reviewed reported higher median NTproBNP
57 concentration in cats with cardiogenic respiratory distress.⁷⁻¹⁰ The one study investigating NTproANP
58 reported that the overall accuracy of this test was lower than NTproBNP, but despite this, the test was
59 still useful to detect cardiogenic dyspnea.⁸ Published NTproBNP cut-off values for identifying cats with
60 acute congestive heart failure range from 214-277 pmol/L, with a sensitivity generally over 85% and a

61 specificity of 84-88%. However, because these studies were published over a 5 year time frame and
62 used 3 different commercially available assays, the cut-off values and sensitivity/specificity data
63 should not be directly compared. Also, recent changes in commercial assay methodology may mean
64 that established cut-off values are replaced by new publications using contemporary assays. Despite
65 this, the evidence convincingly supports the use of NTproBNP to differentiate between cardiac and
66 non-cardiac causes of respiratory distress in cats. A significant practical limitation of the published
67 literature is the current lack of studies investigating the utility of a patient-side NTproBNP test, which
68 has only recently become available.

69

70 **Pleural fluid and urinary NTproBNP measurement**

71 In humans, NTproBNP concentration can be accurately measured in pleural fluid and urine.^{11, 12} The
72 same has been shown in 40 cats presenting to an emergency department with pleural effusions.¹⁰ In
73 both urine and pleural effusion samples, NTproBNP was detectable with adequate performance.
74 NTproBNP concentration was significantly higher in pleural fluid than in plasma with a strong
75 correlation between measurements, suggesting that measurement of NTproBNP in pleural fluid
76 obtained during therapeutic thoracocentesis is an adequate and reliable substitute for blood
77 sampling, thereby reducing handling of these dyspneic patients. Urine NTproBNP to creatinine ratio
78 was higher in the cats with cardiogenic pleural effusion than those with noncardiac causes. Despite
79 this, further analysis failed to determine useful cut-off values to distinguish between cardiac and
80 noncardiac patients using urinary NTproBNP, possibly related to variable handling or processing time
81 for urine samples in the study. Further studies with improved standardisation of urine sample
82 collection from cats with suspected cardiac disease are needed.

83

84 **Identification of cats with occult cardiomyopathy**

85 Occult heart disease is common in cats, and currently most cats are screened by a veterinary
86 cardiologist using echocardiography. However, some cat owners may be reluctant to travel or pay for
87 a cardiologist to perform echocardiography, highlighting a possible role for cardiac biomarkers to pre-
88 screen for cats most likely to benefit from echocardiography. Eleven published studies compared a
89 control group of healthy cats to a group of cats with echocardiographic evidence of heart disease, but
90 no clinical signs of congestive heart failure^{3, 13-21} (Table 3). Of these, only the 2 largest studies were
91 specifically designed to test the ability of cardiac biomarkers to identify occult cardiomyopathy in a
92 screened population of cats. One investigated the use of a quantitative NTproBNP assay,¹⁶ whilst the
93 second evaluated a patient-side SNAP colorimetric assay.²¹ In all, the 10 published studies describe a
94 total of 393 healthy cats, 350 cats with HCM, 38 with RCM or UCM, 5 with DCM and 1 with ARVC.
95 Broadly, all but one of these studies reported that cardiac biomarkers were significantly higher in cats
96 with echocardiographic evidence of cardiomyopathy than in cats without cardiac disease.

97 In three studies, NTproANP was reported to be significantly higher in cats with echocardiographic
98 evidence of heart disease than healthy controls in 3 studies.¹⁸⁻²⁰ In contrast, one small study¹⁷ did not
99 detect a significant difference between cats with and without heart disease but reported a weak
100 positive correlation between NTproANP and left atrial size.

101 NTproBNP has been reported to be significantly higher in cats with heart disease than healthy cats in
102 all 5 studies reporting this comparison. Three studies report an optimal NTproBNP cut-off value for
103 detecting occult cardiomyopathy: 2 studies identified 100pmol/L (71-92% sensitivity, 94-100%
104 specificity),^{15, 16} the third identified 49pmol/L (sensitivity 100%, specificity 89%).¹⁹ However, in those
105 studies that tested the ability of NTproBNP to distinguish between different grades of severity of
106 cardiomyopathy,^{14-16, 21} this biomarker was less accurate at identifying mild grades of disease. This
107 suggests that echocardiography remains preferable to screen for mild/early stage disease. In one
108 study, Maine Coons positive for the MYBPC3:A31P mutation had significantly higher NTproBNP than
109 mutation-negative cats.¹⁴

110 Both studies comparing cTnI in cats with heart disease (no heart failure) to healthy controls reported
111 that circulating concentrations of this biomarker were significantly higher in cats with heart disease,^{3,}
112 ¹³ as did a recent validation study for a high sensitivity cTnI assay.²² However, with the larger samples
113 sizes reported and the similarities in results between the published studies, NTproBNP currently
114 seems the better cardiac biomarker to use when screening for occult cardiomyopathy.

115

116 **Effects of systemic disease**

117 In humans, circulating cardiac biomarker concentrations are known to be influenced by age, sex, renal
118 and thyroid function, body condition (especially obesity) and the presence of anemia.²³ Although the
119 effects of body weight, age and sex have not been well studied in cats, the effects of some non-cardiac
120 diseases have been investigated. Six published studies evaluated the effects of non-cardiac, non-
121 respiratory disease on circulating cardiac biomarkers (Table 4). Three investigated hyperthyroid
122 cats,²⁴⁻²⁶ 2 investigated chronic kidney disease (CKD, plus/minus hypertension),^{27,28} and 1 reported
123 preliminary data in anaemic cats.²⁹ All 3 studies regarding the effect of hyperthyroidism provided
124 strong evidence that NTproANP (n=61),²⁵ NTproBNP (n=84)^{25, 26} and cTnI (n=46)^{24, 26} are increased in a
125 hyperthyroid state and return to the same level as non-hyperthyroid controls after restoration of a
126 euthyroid state by radioactive iodine therapy. Only one of these studies²⁶ compared hyperthyroid cats
127 to separate control groups of normal cats and a separate group of cats with cardiomyopathy. In this
128 study, both NTproBNP and cTnI were higher in cats with cardiomyopathy than hyperthyroidism, but
129 significant overlap was present between groups, suggesting that neither biomarker can effectively
130 differentiate between cats with hyperthyroidism and primary cardiomyopathy. The consistent finding
131 that cTnI is increased in hyperthyroid cats suggests that not only are cardiac filling pressures affected
132 by changes in systemic vascular resistance and circulating volume induced by the endocrinopathy, but
133 that thyrotoxicosis affects the myocardium on a cellular level to cause myocardial cell damage (either

134 by a direct effect of thyroid hormones or an indirect effect, for example via sympathetic nervous
135 system activation).

136 In cats with azotemic CKD, cTnI is commonly higher than the reference interval for healthy cats.
137 However, no correlation between the severity of azotemia and the degree of cTnI elevation was
138 present, suggesting that the azotemic state may be more important than the degree of renal
139 functional impairment when comparing individual cats to reference intervals.²⁷ However, the results
140 of this study merit some additional research, because no control group was used and none of the 14
141 cats investigated had echocardiography performed.

142 Natriuretic peptides have also been evaluated in cats with CKD. One study reported values of
143 NTproANP and NTproBNP in cats with CKD (with and without hypertension) and compared them to a
144 control group of non-hypertensive cats without evidence of CKD.²⁸ NTproBNP was significantly higher
145 in cats with severe azotemia (>440umol/L or 5mg/dL) than those with less severe CKD and healthy
146 controls but, again, no correlation with creatinine concentration was detected. Also, NTproBNP was
147 higher in hypertensive CKD than non-hypertensive cats with CKD, and circulating concentrations
148 reduced after successful treatment of hypertension. Similarly to NTproBNP, NTproANP was higher in
149 severely azotemic cats and those with hypertension. However, unlike NTproBNP, NTproANP did
150 not correlate with serum creatinine concentration and did not normalise with treatment of systemic
151 hypertension. The reasons for these differences are unclear, but this and the findings of several other
152 studies suggest that NTproBNP is more sensitive to dynamic changes than NTproANP. As with the cTnI
153 study above,²⁷ this study of natriuretic peptides in cats with CKD did not include echocardiographic
154 examination of any of the subjects. Also, the control group was not age-matched with the
155 hypertensive and non-hypertensive CKD groups. These weaknesses mean that further, prospective,
156 standardised studies in cats with CKD ± hypertension are warranted, where echocardiography is
157 performed to account for the presence of occult cardiac disease and where a control group is age- and
158 sex-matched to the cats with CKD.

159 One recent study investigating the effect of anemia on cTnI in cats showed that anemic cats had
160 significantly higher circulating cTnI than a control population of unwell, non-anemic cats.²⁹ However,
161 this study was subject to similar methodological flaws, in that echocardiography was not performed
162 on all cats and the authors did not report the frequency with which auscultated abnormalities (such
163 as a gallop sound, arrhythmia or murmur) were present in the anaemic group. Cats with auscultated
164 abnormalities were, however, excluded from the control group of non-anaemic cats.

165

166 **Point of care tests**

167 Much interest has been expressed in developing patient-side cardiac biomarker assays, primarily for
168 use in cats with respiratory distress, in the hope that this may help practitioners more confidently
169 diagnose and treat acute congestive heart failure (CHF). Another potential application for these in-
170 clinic tests would be to help primary clinicians stratify cats with heart murmurs, according to which
171 are most likely to have occult cardiomyopathy and therefore require echocardiography. Two studies
172 evaluating patient-side cardiac biomarker tests in cats with cardiac disease have been published.^{6, 21}

173 The performance of the first patient-side NTproBNP ELISA (IDEXX Ltd) was tested in a recent study of
174 146 cats.²¹ The ability of this colorimetric test to identify cats with moderate to severe heart disease
175 amongst a population of cats referred for cardiac investigation suggested a good performance in
176 identifying moderate and severe grades of occult heart disease. The assay had a positive cut-off
177 NTproBNP concentration of between 108-122pmol/L, similar to the cut-off of 100pmol/L for detection
178 of moderate/severe occult cardiomyopathy previously reported.¹⁶ The negative predictive value (NPV)
179 of the patient-side test was 94%; i.e. in a cat with a negative test result, there was a 94% probability
180 that this patient truly did not have moderate to severe heart disease. Although the positive predictive
181 value (PPV) was only 64%, this also aids identification of a population of asymptomatic cats where
182 echocardiography is indicated to screen for occult disease. These figures suggest that the patient-side

183 test has significantly greater utility to “rule-out” more advanced heart disease than it does to confirm
184 the presence of disease. The population described in this study had a high prevalence (24%) of
185 moderate-severe heart disease. In a different population of lower prevalence, such as the background
186 general practice population, the PPV would be even lower. Importantly however, the NPV of the test
187 would increase. For example, if screening a population of shelter cats for hypertrophic
188 cardiomyopathy (HCM), which has an estimated overall prevalence of 15%,³⁰ the NTproBNP point of
189 care test would have a PPV of 49% and an NPV of 97%, presuming the same test sensitivity and
190 specificity. This would make it a useful test for identifying cats with none or mild disease, for which
191 further diagnostic interventions such as echocardiography are unlikely to add significant additional
192 information to the practitioner. A notable exception to this would be when screening cats used for
193 breeding, where echocardiography would still be required to detect mildly affected cats. Also, the
194 confounding influence of hyperthyroidism to increase circulating NTproBNP concentration should be
195 considered in older cats where point-of-care testing is performed.^{25, 26}

196 To date, the ability of this point of care NTproBNP test to distinguish between cardiac and noncardiac
197 causes of respiratory distress has not been evaluated. Despite this, it is reasonable to assume that a
198 negative colorimetric test in a dyspneic cat is likely to reflect a noncardiac cause of clinical signs. In
199 contrast, patient-side cTnI analysis has been investigated in 37 cats to identify cats with a cardiac cause
200 of acute respiratory distress.⁶ In this study, cTnI was significantly higher in cats with cardiac disease
201 than those with a respiratory cause of dyspnea. Cats with a circulating cTnI concentration below
202 0.24ng/mL all had a noncardiac cause of clinical signs, whereas above 0.66ng/mL all cats had
203 cardiogenic dyspnea. In this population, none of the cats had sepsis such as pyothorax as a cause of
204 dyspnea. Sepsis is known to increase circulating cTnI concentrations in humans and dogs³¹⁻³³ and the
205 same may be true in cats. If so, the findings of this study may not be applicable to a wider population
206 of cats which included patients with pyothorax.

207

208 **Prognostic utility of cardiac biomarkers**

209 In humans, NTproBNP, cTnI and cTnT have been used to stratify patients with HCM according to
210 prognosis.³⁴⁻³⁸ Three studies have been published investigating the association of cardiac biomarker
211 concentration with outcome in cats with heart disease; one investigating NTproANP,³⁹ one
212 investigating both cTnI and cTnT,⁴⁰ and one investigating NTproBNP and cTnI (Table 5).⁴¹

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

221 Cardiac troponins may be more useful than natriuretic peptides in providing prognostic information
222 in cats. The circulating concentration of cTnI and cTnT at diagnosis were significantly higher in cats
223 that suffered cardiac death than survivors in one recent study investigating 36 cats with HCM.⁴⁰ cTnT
224 was a better prognostic marker in this study, with cTnI showing no additional prognostic utility. Results
225 also suggested that serial biomarker monitoring may be clinically useful, because cTnT measurement
226 repeated before the end of the follow-up period in this cohort of cats provided independent
227 prognostic information, even when accounting for cTnT concentration at the time of diagnosis. A
228 second study, reporting 41 cats with HCM, identified this same association between increased cTnI
229 and a greater risk of cardiac death.⁴¹ Cats with a circulating concentration of cTnI >0.7ng/ml at the
230 time of diagnosis had a shorter time to cardiac death, independent of both clinical signs of congestive
231 heart failure and echocardiographic measures of left atrial size or function. In this study, cats with
232 regional LV hypokinesis detected on echocardiography had significantly higher cTnI than cats without

233 regional hypokinesis, possibly reflecting an association between increased cTnI and regional
234 myocardial ischemia or infarction. It is worth noting that these two studies^{40, 41} used different cTnI
235 assays, so despite the similar patient demographics and the publication of these two articles within
236 months of one another, reported cTnI values are not comparable.

237 Currently, no published studies have thoroughly evaluated how cardiac biomarkers may change over
238 time in cats with cardiomyopathy. One recently presented research abstract⁴² suggested that a >70%
239 change in quantitative NTproBNP measurement was required to indicate a genuine change, instead
240 of day-to-day biological or assay variability. In our own clinics, it is advised that an increased
241 NTproBNP test (or positive patient-side SNAP test) be followed up with echocardiography rather
242 than re-testing, so our personal experience with this is limited. In dogs, the rate of change in cardiac
243 biomarker concentration appears important in long-term prognosis, but this has not been reported
244 in cats and it is not understood how this may help to predict outcome in feline patients.

245

246 **Limitations**

247 Most of the studies reviewed here had a prospective design and investigative protocol was
248 standardized where possible. However, treatment protocols were not standardized and differences in
249 decision making between different veterinarians and different owners will no doubt have affected
250 survival time in studies evaluating prognosis.

251 No consensus exists amongst veterinary cardiologists as to how best grade severity of cardiomyopathy
252 in cats, other than to say most cats that have experienced clinical signs of congestive heart failure have
253 severe disease. In the screening studies reviewed here, where cats with cardiomyopathy were
254 classified into groups of equivocal, mild, moderate and severe by some studies, this lack of consensus
255 means that different authors classified cats in different ways. For example, severe cardiomyopathy in
256 some groups took into account left atrial size but in others only accounted for degree of wall

257 thickening. As a result, cats classified as “severe” by some studies may have been classified as
258 “moderate” by others. This lack of consensus means that the reader cannot directly compare the
259 findings of different screening studies utilising cardiac biomarkers. In addition, a lack of consensus and
260 an inconsistency in the echocardiographic measurement technique between veterinary cardiologists
261 means that even the current ‘gold-standard’ of diagnosing mild (or equivocal) HCM may not be reliably
262 comparable between publications, and this may account for some of the differences in optimal
263 NTproBNP cut-off values reported in different studies.

264 Misclassification of patients into even broad groups is possible, such as presence or absence of cardiac
265 disease, or suffering a cardiac versus noncardiac death. An example of this was identified by Humm
266 and colleagues,¹⁰ who reported a suspected misclassification of one cat in their study, despite all
267 patients having been assessed by a veterinary cardiologist using echocardiography. This may have led
268 to falsely low specificity of pleural fluid NTproBNP to detect cardiogenic pleural effusion in their article.
269 Other studies did not perform echocardiography on all cats included, so the presence of cardiac
270 disease in many patients was not assessed, and some studies did not exclude patients with systemic
271 hypertension or hyperthyroidism from their cardiac disease group. Although a heterogeneous
272 population of cats is more likely to be reflective of the wider general practice population,
273 misclassification of cases and the presence of concurrent systemic disease affecting the cardiovascular
274 system are likely to reduce the discriminative ability of the cardiac biomarker tests reported in certain
275 studies. This is especially true in studies with a small sample size or low event rate, such as is the case
276 in many veterinary studies.

277 Finally, two aspects of laboratory technique are important to consider. The use of different assays in
278 different studies limits the utility of published cut-off values to clinicians comparing their measured
279 biomarker concentration to those reported in the literature. This is especially important to note for
280 cTnI, where 5 different assays were used across the 13 papers reviewed here. Another limitation is
281 the difference between NTproBNP concentration measured by the “second generation” IDEXX Feline

282 Cardiopet NTproBNP assay and the previous assay used by the same laboratory (although the
283 manufacturer states that values are likely to be comparable). It is likely that studies published before
284 2014 did not use the more sensitive second generation NTproBNP assay from IDEXX, so cut-off values
285 may not apply to practitioners testing cats at the time of writing, even though they are using the same
286 reference laboratory.

287

288 **Summary**

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

293 NTproBNP appears to most reliably differentiate between cardiac and noncardiac causes of
294 respiratory distress in cats. Measurement of NTproBNP is reliable from pleural fluid obtained by
295 thoracocentesis, without the need for blood sampling restraint in an unstable patient. The patient-
296 side test will increase the convenience of NTproBNP testing in cats in general practice and this test has
297 great potential to assist in the emergency room. However, the usefulness of NTproBNP in
298 prognostication is limited where left atrial dilation and a history of congestive heart failure can be
299 reliably confirmed. In contrast, measurement of cTnI can be used not only as a patient-side test to
300 differentiate cardiac from noncardiac causes of respiratory distress (albeit less accurately than
301 NTproBNP), but can also be used as part of prognostication together with heart failure status and
302 echocardiographic measurements.

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

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

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

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

320

321 **Conflicts of Interest**

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

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

Search term	Feline
	Cat
	Natriuretic
	Peptide
	Cardiac
	Troponin
	NTproBNP
	NT-proBNP
	NTproANP
	NT-proANP
	cTnI
	cTnT
	Cardiomyopathy
	Biomarker

328

329

330 **Table 2:** Summary of the studies reporting the use of cardiac biomarkers to differentiate between
 331 cardiac and noncardiac causes of respiratory distress in cats

332 *cTnl, cardiac troponin I; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; AUC,*

333 *area under the curve, pertaining to receiver operating curve statistical analysis of diagnostic test utility; P, prospective study design; M,*

334 *multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E, echocardiography on all cats*

Biomarkers	Number of cats	Conclusions	Assay	Citation	Evidence category
cTnl	16 cats with HCM, 18 healthy controls	cTnl can help distinguish between HCM and non-HCM groups, but less able to identify cats with CHF	Immulyte (Diagnostic Products Co.)	Connolly ³	P;C;E
	43 cats with dyspnea (31 cardiac)	Able to identify cardiac causes of dyspnea: AUC 0.84. Overlap between groups	Stratus (Dade Behring)	Herndon ⁴	P;M;C;E
	53 cats with dyspnea (23 cardiac)	Significant difference between cardiac and noncardiac: AUC 0.84. Overlap between groups	Immulyte (Siemens Medical Diagnostics)	Connolly ⁵	P;M;C
	39 dyspneic cats (25 cardiac) 37 healthy controls	A patient-side cTnl assay can be used to differentiate cats with cardiac causes of dyspnea from those with noncardiac disease and normal controls	i-Stat 1 analyser (Heska Corp.)	Wells ⁶	P;M;C;E
NTproANP NTproBNP	85 dyspneic cats (44 cardiac)	Both NTproANP and NTproBNP were able to discriminate between cardiac and noncardiac patients, but NTproBNP better performance (cut-off 220pmol/L, AUC 0.96)	proANP 1-98 (Guildhay Ltd), Cardioscreen NTproBNP (Guildhay Ltd)	Connolly ⁸	P;C;B

NTproBNP	162 dyspneic cats (101 cardiac)	Reliable discrimination between cardiac and respiratory causes of dyspnea: cut-off 207pmol/L, AUC 0.98	CardioPet proBNP (IDEXX Ltd)	Fox ⁷	P;M;C;E
	21 cats with pleural effusion (11 cardiac disease)	NTproBNP successfully discriminated between cardiogenic and noncardiac causes of pleural effusion: cut-off 258pmol/L, AUC 1.0	Cardiopet proBNP (IDEXX Ltd)	Hassdente -ufel ⁹	P;C;B;E
	40 cats with pleural effusion (22 cardiac)	Plasma NTproBNP reliably identified cats with cardiogenic pleural effusion: cut-off 214pmol/L, AUC 0.91	Vetsign Feline Cardiopet NTproBNP (IDEXX Ltd)	Humm ¹⁰	P;C;E

335

336

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

339 *cTnl*, cardiac troponin I; *NTproANP*, N-terminal pro atrial natriuretic peptide; *NTproBNP*, N-terminal pro B-type natriuretic peptide; *AUC*,
 340 area under the curve, pertaining to receiver operating curve statistical analysis of diagnostic test utility; *P*, prospective study design; *M*,
 341 multicenter recruitment; *C*, control group appropriate; *B*, blinding specified in manuscript; *E*, echocardiography on all cats

Test	Number of cats	Conclusions	Assay	Citation	Study design
cTnl	16 cats with HCM, 18 healthy controls	cTnl can help distinguish between HCM and non-HCM groups, but less able to identify cats with CHF	Immulyte (Diagnostic Products Corp.)	Connolly ³	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	Status CS troponin I (Dade Behring Inc.)	Herndon ¹³	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)	ADVIA Centaur CP Tnl-ultra (Siemens)	Langhorn ²²	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	proANP 1-98 Biomedica, (American Laboratory Products Co.)	Maclean ¹⁷	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	Shinonoria-ANP radioimmunoassay (Shionogi Co.)	Hori ¹⁸	P;C;E
	43 cats: 16 heart disease/CHF, 16	Positively correlated with LA size. Discriminated between all 3 groups	proANP 1-98 (Biomedica)	Zimmering ²⁰	P;B;C;E

	heart disease/NO-CHF, 11 controls		Group, Immundiagnostik AG)		
NTproANP NTproBNP	78 cats: 33 heart disease/CHF, 17 heart disease/NO-CHF, 28 controls	Both biomarkers distinguished between all 3 groups, and were correlated with each other. NTproBNP was more accurate at detecting cardiac disease: cut-off 49pmol/L, AUC 0.98. Both markers positively correlated with LA size and E:E' ratio.	proANP 1-98 (Guildhay Ltd) Feline Cardioscreen proBNP (Guildhay Ltd)	Connolly ¹⁹	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. Severe HCM cut-off 44pmol/L, AUC not reported. MYBPC3:A31P mutation positive cats had higher NTproBNP	Feline Cardiocare NTproBNP (Veterinary Diagnostics Institute)	Hsu ¹⁴	P;C;E
	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. Severe HCM had significantly higher NTproBNP than other groups. Cut-off for mild HCM detection 100pmol/L, AUC 0.96	Feline Cardioscreen proBNP (Guildhay Ltd)	Wess ¹⁵	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. Cut-off	Cardiopet proBNP (IDEXX Ltd)	Fox ¹⁶	P;M;C;B;E

		99pmol/L, AUC 0.92. Correlation of NTproBNP with LV wall thickness and LA size.			
	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%	NTproBNP SNAP (IDEXX)	Machen ²¹	P;M;C;B;E

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344 **Table 4:** Summary of the studies reporting the use of cardiac biomarkers in patients with noncardiac
 345 disease

346 *cTnl, cardiac troponin I; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; P,*
 347 *prospective study design; M, multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E,*
 348 *echocardiography on all cats; RAI, radioactive iodine treatment; BP, blood pressure; PCV, packed cell volume*

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Test	Number of cats	Conclusions	Assay	Citation	Study design
cTnl	23 hyperthyroid cats (18 post-treatment with RAI)	cTnl higher in cats with higher total thyroxine concentration. Trend towards reduction in cTnl observed, but not statistically significant.	Immulyte (Diagnostic Products Co.)	Connolly ²⁴	P;B;E
NTproBNP cTnl	23 hyperthyroid cats (12 post-treatment with RAI), 17 cats with HCM, 19 controls	cTnl was increased in 46% and NTproBNP was increased in 38% hyperthyroid cats with no echocardiographic abnormalities. Both biomarkers normalised in most hyperthyroid cats after RAI treatment.	Cardiopet NTproBNP (IDEXX), Stratus CS Stat cTnl (Dade Behring)	Sangster ²⁶	P;C;B;E
NTproANP NTproBNP	85 hyperthyroid cats at baseline, 61 post-treatment with RAI	Hyperthyroidism was associated with a significant but modest elevation of both natriuretic peptides, which reduced after RAI treatment.	Cardiopet NTproBNP (IDEXX)	Menaut ²⁵	P;M
cTnl	14 cats with CKD	cTnl higher in azotemic patients, but no correlation with creatinine concentration	Stratus CS Stat cTnl (Dade Behring)	Porciello ²⁷	

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.	NTproANP 1-98, (Biomedica Gruppe), VETSIGN Feline Cardio-SCREEN proBNP, (Guildhay Ltd)	Lalor ²⁸	M;C
cTnl	49 cats: 18 anemic, 31 non-anemic, unwell controls	cTnl higher in anemic cats than controls, but no correlation with PCV	Immulite (Siemens)	Lalor ²⁹	P;C

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

352 *cTnI, cardiac troponin I; NTproANP, N-terminal pro atrial natriuretic peptide; NTproBNP, N-terminal pro B-type natriuretic peptide; P,*

353 *prospective study design; M, multicenter recruitment; C, control group appropriate; B, blinding specified in manuscript; E,*

354 *echocardiography on all cats*

Test	Number of cats	Conclusions	Assay	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.	proANP 1-98 (Biomedica Group, Immundiagnostik AG)	Zimmering ³⁹	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	ADVIA Centaur CP TnI-ultra (Siemens), Elecsys hs-TnT (Roche)	Langhorn ⁴⁰	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	Cardiopet NTproBNP (2 nd Gen; IDEXX), AccuTnI (Beckman Coulter)	Borgeat ⁴¹	P;B;E

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Footnotes

357 ^a <http://www.ncbi.nlm.nih.gov/pubmed>

358 ^b <http://wok.mimas.ac.uk/>

359 ^c [http://scholar.google.com /](http://scholar.google.com/)

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