



Low plasma taurine levels in English Cocker Spaniels diagnosed with Dilated Cardiomyopathy

Journal:	<i>Journal of Small Animal Practice</i>
Manuscript ID	JSAP-2020-0192.R3
Manuscript Type:	Original Paper
Keywords:	Cardiac, Dogs, Amino acid, Deficiency, Supplementation, Concentration

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1 Abstract (233 words)

2

3 *Objective:* Dilated cardiomyopathy (DCM) has been documented in Cocker Spaniels.

4 American Cocker Spaniels (ACS) with taurine deficiency and DCM phenotype

5 improved following taurine supplementation. No studies have been performed

6 investigating taurine deficiency in English Cocker Spaniels (ECS). The aims of this

7 study were to evaluate taurine levels in ECS with DCM and assess their survival time

8 and natural progression of their disease.

9

10 *Methods:* Retrospective comparison of ECS with DCM phenotype with and without

11 taurine deficiency at the cardiology department of a UK academic referral centre

12 between 2008 and 2018.

13

14 *Results:* Taurine plasma concentration was available in 16 ECS with DCM

15 phenotype; 13/16 of which had congestive heart failure and 3/16 of which did not.

16 Taurine concentration was low (<50 µmol/L) in 13/16 and normal in 3/16. Deficient

17 dogs received taurine supplementation in addition to conventional cardiac

18 medications. Eight dogs were still alive at the end of this study and 8 were dead.

19 MST for all dogs included in the study was 2800 days. Left ventricular (LV) systolic

20 function improved and LV dimensions reduced in ECS with taurine deficiency

21 following taurine supplementation and conventional cardiac therapy, although similar

22 results were observed in ECS with normal taurine concentration on cardiac therapy

23 alone.

24

25 *Clinical importance:* Based on laboratory reference intervals, low taurine
26 concentrations were common in ECS with DCM, showing a possible association
27 between DCM in ECS and taurine deficiency; supplementation with taurine was not
28 curative.
29

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30 **WORD COUNT: 4157**

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32 **Introduction**

33

34 Dilated cardiomyopathy (DCM) is the most common acquired myocardial disease in
35 dogs (Fox *et al.* 1999). Echocardiography is the gold standard for diagnosis:
36 decreased systolic function leads to renin-aldosterone-angiotensin system (RAAS)
37 activation and ventricular dilation which may eventually result in congestive heart
38 failure. Left atrial enlargement and arrhythmias may also be present (Dukes-McEwan
39 *et al.* 2003). The preclinical or occult phase of the disease is characterized by
40 chamber dilation with reduced systolic function and possible arrhythmias with no
41 clinical signs (Dukes-McEwan *et al.* 2003). Medical treatment varies depending on
42 the phase. Pimobendan is recommended for occult DCM (Summerfield *et al.* 2012),
43 but once clinical signs of CHF develop, addition of diuretics and potentially ACE
44 inhibitors and spironolactone, is indicated (Dukes-McEwan 2000; Luis Fuentes *et al.*
45 2002). Any haemodynamically significant arrhythmias may also require treatment.

46

47 Primary (idiopathic) DCM has been documented in a number of breeds including
48 English cocker spaniel (ECS) (Gooding *et al.* 1982, 1986; Thomas 1987; Tidholm *et*
49 *al.* 1997). In a large UK survey of dogs presenting with DCM, ECS was the fourth
50 most common breed affected, with 30/369 cases and was reported to have longer
51 survival times compared with other breeds (Martin *et al.* 2009).

52

53 The DCM phenotype may be a consequence of heritable genetic mutations, viral
54 infections, immune-mediated disorders, arrhythmias, toxins and nutritional
55 deficiencies (Van Vleet and Ferrans, 1986; Cunningham *et al.*, 1992; Shinbane *et al.*,

56 1997; Backus *et al.* 2006). Due to familial disease, a genetic basis is suspected in
57 some breeds and already documented in others, including ECS (Thomas 1987), as
58 recently reviewed by Dutton & Lopez-Alvarez (2018). Prior to making the diagnosis
59 of DCM, other conditions which may result in similar echocardiographic changes
60 must be actively excluded.

61

62 Taurine deficiency has been implicated as a nutritional cause of a DCM phenotype.
63 This was initially reported in a group of cats affected by DCM, where the phenotype
64 completely reversed with taurine supplementation; prior to this discovery, the
65 prognosis for cats with DCM caused by taurine deficiency was grave (Pion *et al.*
66 1987). Later, American Cocker Spaniels (ACS) with low taurine concentrations were
67 also reported to at least partially reverse their DCM phenotype after both taurine and
68 L-carnitine supplementation (Kittleson *et al.* 1997). Other studies reported similar
69 findings, in this and other breeds such as Golden Retrievers (Kramer *et al.*, 1995;
70 Gavaghan & Kittleson 1997; Kaplan *et al.*, 2018; Ontiveros *et al.*, 2020).

71

72 English cocker spaniels were imported into the United States in the 19th century:
73 ACS were developed and eventually recognized as a different breed in 1936 (Fogle
74 1996). Therefore, there is likely to be a genetic relationship between the ACS studied
75 by Kittleson and colleagues (1997) and the ECS population. To the authors'
76 knowledge, no studies have been reported investigating taurine deficiency in ECS
77 with DCM.

78

79 The main aim of this study was to investigate a possible association between taurine
80 deficiency and DCM in ECS in the UK. The hypothesis was that ECS with a

81 diagnosis of DCM could also have low taurine levels, similar to ACS. Additional aims
82 of this study were to investigate the response to taurine supplementation in deficient
83 ECS and document the progression of DCM and survival times in this breed.

84

85 **Materials and methods**

86 This was an observational, retrospective study. Cases were retrieved from a single
87 multidisciplinary referral hospital in the UK.

88 The hospital database was searched for ECS examined by the cardiology service
89 between 2008 and 2018 and diagnosed with DCM. Dogs were included if retrieved
90 data included both a complete echocardiographic examination and plasma taurine
91 concentration. All dogs had indirect assessment of systolic blood pressure (Doppler
92 method). Routine blood work (haematology, biochemistry, thyroid function
93 assessment) was carried out if the clinician considered it relevant to the
94 investigations for each patient.

95

96 Dogs with other concurrent cardiac conditions were excluded. Dogs with clinical
97 signs, blood pressure or clinical pathology results indicating significant systemic
98 disease, including systemic hypertension, were excluded. Systemic hypertension
99 was defined as >160mmHg on repeated measurements on more than one occasion,
100 in accordance with the ACVIM guidelines (Acierno *et al.* 2018).

101 Dogs affected by hypothyroidism, on treatment with levothyroxine, were included
102 provided that the dog had been receiving treatment for over 2 months prior to
103 inclusion and the condition was considered stable on medical therapy, [similar to the](#)
104 [criteria described by Summerfield *et al.* \(2012\).](#)

105

106 From the patient records, the following data were retrieved: weight, age, gender,
107 neuter status and echocardiography results. Electrocardiograms and results were
108 reviewed, if available. Laboratory data (biochemistry and haematology) were
109 reviewed, where available, to exclude concurrent conditions. Medications and doses
110 prescribed for each patient were also retrieved.

111 For taurine analysis, heparinised plasma samples were submitted to IDEXX (Referral
112 assay via IDEXX Laboratories, Wetherby, United Kingdom). Samples were
113 centrifuged and plasma separated within 30 minutes of the blood sample being
114 taken. Taurine deficiency was defined as concentrations $<50 \mu\text{mol/L}$, based on the
115 laboratory's reference range interval (50-180 $\mu\text{mol/L}$); these were extrapolated from
116 the MUST study (Kittleson *et al.*, 1997) and were also confirmed in others studies that
117 included various breeds (Kramer *et al.*, 1995; Delaney *et al.*, 2003; Tôrres *et al.*,
118 2003).

119
120 Doppler Echocardiographic examinations were carried out using a GE Vivid 7
121 (Buckinghamshire, UK) machine, using a 7S or M4S transducer. The dogs were in
122 lateral recumbency on a purpose-designed table to allow imaging via the dependent
123 thoracic wall. Studies have been performed by either a cardiology diplomate or a
124 cardiology resident under the direct supervision of a diplomate. Two dimensional
125 (2D) and M-mode images were acquired, recorded and measured according to
126 standard protocols (Sahn *et al.* 1978; Thomas *et al.* 1994; Boon 1998). Data from the
127 M-mode studies retrieved included left ventricular internal dimensions both in
128 diastole (LVIDd) and systole (LVIDs); fractional shortening (FS) was calculated. The
129 M-mode LV diameters were normalised for body weight by allometric scaling in
130 diastole (LVIDDN) and systole (LVIDSN) (Cornell *et al.* 2004). The mitral E point to

131 septal separation (EPSS) measurement from mitral valve M-mode was also
132 recorded. From the 2D right parasternal long axis 4 chamber view optimizing the left
133 ventricular length and area, Simpson's method of discs was used to determine LV
134 end-diastolic and end-systolic volumes. Ejection fraction (EF), and sphericity index
135 were calculated (Dukes-McEwan *et al.* 2003). The end-systolic and end-diastolic
136 volumes indexed to body surface area (BSA) were also calculated (LVESVi and
137 LVEDVi respectively). The BSA was calculated using the standard formula (Ford &
138 Mazzaferro 2011). Maximal left atrial diameter, measured at the end of ventricular
139 systole from a right parasternal long-axis 4 chamber view and the short axis ratio of
140 the left atrium to aortic diameters, measured at the end of diastole, were recorded
141 (Chetboul & Tissier 2012). Colour flow and spectral Doppler were used to exclude
142 other significant cardiac diseases. Mitral regurgitation was accepted provided it was
143 a central jet implying origin due predominantly to stretch of the mitral annulus, rather
144 than primary mitral valve disease (myxomatous or dysplastic); dogs with markedly
145 thickened or prolapsing mitral leaflets were not included. Colour flow and spectral
146 Doppler transvalvular flows were documented, but not analysed further for purposes
147 of this study.

148 Repeated echocardiographic studies were obtained at a frequency determined by
149 the attending clinician, and the echocardiographic data were retrieved from every
150 available examination.

151

152 Congestive heart failure was defined as left-sided if there were compatible
153 radiographic findings, when available; in the absence of radiographs,
154 echocardiographic signs of increased left filling pressures (Schober *et al.*, 2010) in
155 association with clinical signs and response to furosemide administration were

156 considered supportive of CHF. Radiographs had been reviewed and reported by
157 diagnostic imaging diplomates or diagnostic imaging residents working under
158 supervision of a diplomate.

159

160 If dogs had plasma taurine level $<50 \mu\text{mol/L}$, supplementation with taurine was
161 commenced. Dogs with CHF or with preclinical DCM were treated according to the
162 individual clinician and owner preference. Drugs used and their doses were
163 recorded.

164

165 Survival time was calculated from the time of initial diagnosis of DCM and taurine
166 assay to death. Cardiac deaths were defined as sudden death or euthanasia
167 because of cardiac reasons. Other causes of death were categorised as non-
168 cardiac. Dogs lost to follow-up were censored.

169

170 Statistical analysis

171 All analyses were performed with Graphpad Prism 7 (GraphPad Software, Inc, La
172 Jolla, California, US). Data were inspected graphically for normality of distribution
173 and tested for normality with a Shapiro-Wilk test. Continuous data are presented as
174 mean \pm standard deviation when normally distributed, or as median and interquartile
175 range (IQR; 25th – 75th percentile) when not normally distributed.

176

177 Survival time was evaluated for dogs with low and normal taurine levels. A Kaplan-
178 Meier curve was constructed. Dogs were right censored if still alive, lost to follow-up
179 or if they had died of non-cardiac disease.

180

181

182 **Results**

183

184 Sixty ECS were evaluated by the cardiology referral service of an academic
185 institution between 2008 and 2018.

186

187 Forty-four dogs were excluded from the study. Thirty-three of these were diagnosed
188 with other cardiac diseases. Eleven dogs were excluded due to insufficient data; of
189 these, 3 dogs were reported to have DCM but no information regarding taurine levels
190 was available.

191

192 Sixteen dogs met the inclusion criteria: 13/16 had low plasma taurine concentration.

193 In the dogs with low plasma taurine, the mean taurine concentration was $17.46 \pm$

194 $11.03 \mu\text{mol/L}$. Three dogs had normal taurine concentrations (75, 81 and 194

195 $\mu\text{mol/L}$). Thirteen dogs were in congestive heart failure. The 3/16 dogs which did not
196 have CHF all had low taurine concentrations.

197 The mean age of the dogs included in the study was 6.75 ± 3.02 years, the mean

198 body weight was $15.3 \text{ kg} \pm 2.7$. There were 11 males and 5 females included. There

199 were 8 males (4 neutered) and 5 females (4 neutered) with low taurine levels. All

200 dogs with normal taurine levels were males (2 neutered). Signalment, taurine

201 concentrations, CHF status and medications including taurine supplementation and

202 outcome at the time of writing are reported for each individual dog in Table 1.

203 Taurine supplementation was started in all dogs with low taurine concentration at a

204 dose of $67.8 \pm 38.9 \text{ mg/kg/day}$. Eleven dogs did not have taurine levels rechecked,

205 though the 2 dogs with low taurine levels that did have further measurements 6

206 months later showed values of 200 and 279 $\mu\text{mol/L}$ (ref. 50-180). All dogs received
207 one or more cardiac medications; 8 dogs were receiving other medications or
208 supplements (Table 1).

209 Two dogs with low taurine concentrations and one with normal taurine levels
210 received clopidogrel due to left atrial spontaneous echocontrast, suspected to
211 represent a hypercoagulable state. The dog with normal taurine also received
212 doxycycline due to the presence of ticks and the fact that tick-borne disease could
213 not be ruled-out. The same dog received sildenafil to treat pulmonary hypertension
214 presumed secondary to left-sided CHF. Another dog with low taurine levels received
215 amlodipine in the attempt of afterload reduction.

216

217 Echocardiographic variables at admission and at follow-up (median 30 days; range
218 7-90) were reported (Table 2). Serial echocardiographic studies were available for
219 10/16 dogs. Comparison between echocardiographic variables at baseline and at the
220 first follow-up are shown (Fig. 1). Figure 2 shows echocardiographic images of one
221 of the dogs with low taurine concentration with dilated left ventricle and poor systolic
222 function before (Fig. 2a-2b) and after (Fig. 2c-2d) taurine supplementation; is
223 improvement of left ventricular dimensions and systolic function at the recheck

224 although statistical comparison was not performed (~~Before: EF: 38%; FS: 11%;~~

225 ~~LVESVi: 102.9 mL/m²; LVIDSN: 2.07; LVIDDN: 2.47. After: EF: 47%; FS: 7%;~~

226 ~~LVESVi: 64.2 mL/m²; LVIDSN: 1.07; LVIDDN: 1.93~~). In all dogs included in the

227 study, there was a subjective improvement between admission and first re-check

228 values of LVESVi, LVIDSN, LVIDDN and EF. The dogs with low taurine levels

229 showed a subjective improvement between admission and re-check values of

230 LVIDSN and LVIDDN, but not in LVESVi and EF. Again, all the above values were

231 not statistically compared due to low numbers and to avoid “testing against
232 baseline”. For the dogs which underwent serial echocardiographic examinations,
233 graphical representation of LVESVi and LVDSN values over time are shown in
234 figures 3a and 3b, respectively (Fig. 3a-b).

235

236 All dogs that died before the end of the study were euthanized due to worsening of
237 their cardiac disease (Table 1). Four dogs were lost to follow-up (all had low taurine
238 concentrations, 3 were in CHF).

239 The median survival time (MST) for all dogs included in the study was 1155 days
240 (195 -2800) (Fig. 4). Dogs with low taurine levels had a MST of 2800 days (790 –
241 upper limit not calculable), whereas those with normal levels had a survival time of
242 14, 90 and 478 days. The 13 dogs in with CHF (10 with low taurine levels and 3 with
243 normal levels) had a MST of 1155 days (478-2800), whereas the two non-CHF dogs
244 survived for 83 and 840 days, respectively (one dog was lost to follow-up).

245

246 Discussion

247

248 Based on our laboratory reference range, we found that taurine deficiency is
249 commonly identified in ECS diagnosed with DCM. However, no clear causal
250 association could be identified in this study; indeed, the study design does not allow
251 causal relationships to be investigated.

252 ~~The serial echocardiographic data shows that taurine supplementation might not be~~
253 ~~curative and taurine deficiency may not be the sole cause of DCM phenotype in this~~
254 ~~breed.~~ In dogs with serial echocardiographic data, we did not carry out any statistical
255 analysis in view of small numbers in this descriptive study. However, data suggest

256 that taurine supplementation might not be curative and taurine deficiency may not be
257 the sole cause of DCM phenotype in this breed. This has also been shown in other
258 breeds such as ACS, Golden retrievers, Newfoundlands and Irish Wolfhounds
259 (Kittleson *et al.* 1997; Fascetti *et al.* 2003; Alroy *et al.* 2005; Bélanger *et al.* 2005;
260 Backus *et al.* 2006; Vollmar *et al.* 2013). In contrast, cats with taurine-deficient~~ey~~
261 DCM have a reversible cardiomyopathy with taurine supplementation (Pion *et al.*
262 1987).

263 We did not measure the whole blood taurine concentrations and these have been
264 reported to be substantially higher than plasma taurine concentrations ~~(Delaney et~~
265 ~~al., 2003)~~. Whole blood taurine concentration may be superior, if available, as it more
266 closely reflects muscle taurine concentration and therefore overall taurine status,
267 whereas plasma taurine may reflect fasting or post-prandial status (Delaney *et al.*
268 2003). For this study, only plasma taurine concentrations could be assayed and no
269 record were made of when each dog's last meal had been taken prior to sampling.

270

271 As mentioned above, no statistical analysis was performed between admission and
272 re-check echocardiography values in order to avoid "testing against baseline",
273 therefore only subjective or visual assessments could be made; however, it is
274 interesting to notice changes that we recorded in our dogs during the study period.

275 As figures 1 a-h and 3 a-b show, at the first follow-up echocardiography values
276 showed reduction in LV diameter and volumes (LVIDd, LVESVi, LVIDDN, LVIDSN)
277 with improved systolic function (EF, LVESVi) if the whole population was considered.
278 However, those with low taurine levels at the re-check, had an improvement in
279 LVIDd, LVIDDN and LVIDSN but not in LVESVi and EF. In line with our data,
280 Kittleson and colleagues (1997) reported that ACS with DCM and low taurine

281 concentrations showed improved systolic function after supplementation. Taurine
282 supplementation may improve systolic function, even in the absence of a taurine
283 deficient state as shown in ~~It~~ a study conducted in people with chronic CHF, where
284 taurine supplementation was given for 6 weeks and a substantial improvement in
285 systolic function was reported (Azuma *et al.* 1992). Therefore, it is possible that
286 taurine supplementation at pharmacological doses, could have played a role in the
287 reduction of the LV chamber dimensions and improvement in systolic function in our
288 population of ECS, even if low-aurine status was not associated with their DCM.
289 Since all ECSs also received conventional cardiac therapy, it is not possible to
290 separate the effects of this medications from taurine supplementation in ECS with
291 low taurine concentrations. Diuretics reduce preload, which will reduce LV size
292 (showed by a reduction in values of LVIDd), as well as resolving fluid retention
293 associated with CHF due to both systolic dysfunction and RAAS activation. It is also
294 well documented that pimobendan reduces ventricular size in both CHF and
295 preclinical DCM patients as well as dogs with mitral valve myxomatous disease
296 (Summerfield *et al.* 2012; Häggström *et al.* 2013; Boswood *et al.* 2016).

297

298 A relationship between taurine deficiency and DCM phenotype in ACS was initially
299 reported by Kramer *et al.* (1995). A few years later, in the multicentred spaniel trial
300 (MUST) study, Kittleson and colleagues (1997) showed an improved systolic function
301 in the breed following supplementation with both taurine and L-carnitine.

302 Unfortunately, the concurrent use of both supplements makes it unclear whether the
303 response observed was due to the concurrent L-carnitine supplementation. In our
304 study, myocardial L-carnitine levels were not assessed, as myocardial biopsies are
305 required for diagnosing carnitine deficiency (Meurs, 2004) and L-carnitine was only

306 supplemented in one dog (dog 4 in Table 1), who died a cardiac death 115 days
307 after diagnosis without a follow-up echocardiography. It is therefore possible that
308 different results may have been achieved if L-carnitine was also routinely
309 supplemented to the low taurine dogs, which would then also allow a direct
310 comparison with the MUST study (Kittleson et al 1997). Indeed, one of the reasons
311 why L-carnitine was started in the MUST study population was because the first 2
312 ACS failed to reach demonstrable improvement with taurine alone, despite normal
313 plasma levels of L-carnitine (Kittleson et al 1997). Taurine synthesis has also been
314 shown to differ between breeds, with large breeds more predisposed to deficiency:
315 groups of Newfoundlands and Golden Retrievers have been reported to have low
316 taurine concentration and a DCM phenotype, which improved after taurine
317 supplementation (Fascetti *et al.* 2003; Bélanger *et al.* 2005; Backus *et al.* 2006).
318 In cats, taurine deficiency can be associated with several potential causes including
319 increased excretion with urine and faeces (Hickman *et al.*, 1992; Edgar *et al.* 1998).
320 In our study, urinary and faecal taurine concentration were not measured. Another
321 explanation for taurine deficiency is related to diet. ~~C~~ and consumption of certain
322 commercial and prescription diets have been implicated with low plasma taurine
323 concentrations in dogs with DCM (Sanderson *et al.* 2001; Fascetti *et al.* 2003;
324 Sanderson, 2006; Ko *et al.* 2007; Kaplan *et al.* 2018).
325 More recently, grain free diets and exotic ingredients have been suspected to be
326 associated with DCM phenotype (Freeman *et al.* 2018) although not always with low
327 taurine concentrations. Unfortunately, we were unable to retrieve diet history for all
328 the ECS due to the retrospective nature and long time-course of our study.
329

330 Two dogs with low taurine levels and one with normal taurine levels received
331 clopidogrel due to the presence of left atrial spontaneous echocontrast. This can also
332 be associated with low velocity blood flow or inflammatory disease and both
333 conditions can lead to thrombus formation. (Spence *et al.*, 2019)

334

335 In this study, ECS affected by DCM and CHF had a MST of 1155 days. ~~This~~ which is
336 ~~much~~ longer than the survival time associated with DCM and CHF reported in ~~the~~
337 ~~literature~~ other breeds. A survival time of 27 days was reported in 189 dogs of various
338 breeds with DCM and CHF whereas a MST of 65 days was found in a group of 37
339 dogs affected by DCM; in both these studies, dogs did not receive pimobendan
340 (Monnet *et al.* 1995; Tidholm *et al.* 1997).

341 More recent data showed a MST of 133 days in 369 dogs of various breeds with
342 DCM (74% in CHF at presentation) (Martin *et al.*, 2009). Dobermanns in CHF were
343 also shown to have a short MST of 50.67 days that increased to 329 days with
344 pimobendan therapy (Luis Fuentes *et al.*, 2002). Dobermanns with preclinical DCM
345 at presentation had times to primary end-point (sudden death or CHF) of 441 days
346 which was shown to increase to 718 days in dogs receiving pimobendan
347 (Summerfield *et al.* 2012). American Cocker Spaniels with DCM and low-aurine in
348 the MUST study (Kittleson *et al.* 1997) had a longer MST (849 days) than that
349 reported in previous studies, but still shorter than our ECS. Data from an
350 unpublished study state a MST of ECS with DCM of 750 days (P. Wotton, 1998)¹;
351 however, taurine levels were not measured in these dogs, nor was it supplemented.
352 In the study by Luis Fuentes (2002), ECS receiving placebo or pimobendan had a

¹ Wotton, P.R., (1998). Cardiomyopathy in English cocker and springer spaniels: A review of 38 cases. Proceedings of the British Small Animal Veterinary Association, p.316.

353 MST of 537 and 1037 days, respectively, showing considerably longer survival time
354 compared to other breeds, which is supported by the results presented here. The
355 most recent comparison of different breeds with DCM showed ECS with DCM to
356 have a MST of 511 days, the longest amongst all the breeds in the study (Pedro *et al.*
357 *al.* 2011). It can be appreciated from these studies that the MST may be longer in
358 ECS, compared with other breeds with DCM.

359 The MST of the dogs with low taurine levels was 2800 days, numerically longer than
360 that reported for ECS with DCM in other publications (511 days, Pedro *et al.* 2011;
361 750 days, Wotton 1998, unpublished data). Dogs from Dr Wotton's historical study
362 did not receive pimobendan, which might explain the shorter MST. Dobermanns with
363 DCM receiving pimobendan showed a longer MST than those on placebo, but the
364 same study did not show a statistically significant improvement in ECS receiving
365 pimobendan. ~~perhaps~~ This may be because they survived for longer regardless of
366 treatment, provided the CHF was controlled (Luis Fuentes *et al.* 2002). ~~Nevertheless,~~
367 ~~e~~ Our results may suggest a response to taurine supplementation, however this was
368 only a subjective improvement in a small population in which it was not appropriate
369 to make statistical comparison.

370 It is possible that once CHF is well managed, ECS may have a more favourable
371 prognosis despite the diagnosis of DCM. ~~although~~ ~~†~~ the low numbers of dogs in the
372 pre-clinical phase may have affected these results.

373

374 Statistical comparison of MST of dogs in CHF and not in CHF, dogs with low taurine
375 levels and normal taurine levels was not performed due to low numbers that would
376 have led to unreliable results.

377

378 **Limitations**

379

380 This study has some limitations due to its retrospective nature. Firstly, we had a
381 small number of cases and this could have affected the reliability of the results. The
382 low numbers of ECS with DCM with normal taurine concentration mean it was not
383 possible to compare aspects about DCM or response to treatment in these dogs and
384 the dogs with low taurine concentrations.

385 We did not compare echocardiographic values between baseline and recheck to
386 avoid "testing against baseline", therefore, the above results should be considered
387 as subjective based on visual assessments of the graphs. The echocardiographic
388 examinations were performed by different operators and inter-operator and inter-
389 observer variability were not assessed as part of this study. However, all
390 echocardiographers had undergone similar training and followed similar acquisition
391 and measurement protocols.

392 Histopathology was not performed in any of the cases included in the study,
393 therefore, the diagnosis was based on echocardiographic findings. We also did not
394 obtain pedigree information from these dogs, so we were not able to investigate for
395 familial DCM, or possible inherited basis for the taurine deficiency. This should be
396 addressed in future prospective studies.

397 Dogs were classified as taurine deficient based on the laboratory reference interval-
398 but breed specific reference range is currently not available. Ideally, taurine
399 concentration should have been tested in a control group of ECS without DCM since
400 it is possible that this breed has different basal plasma taurine levels as

401 demonstrated in Golden Retrievers (Ontiveros *et al.*, 2020). Also, whole blood
402 taurine concentrations were not measured in this study.

403 We did not investigate the type of diet the dogs were fed so we cannot assess the
404 association between diet and DCM in this study (Freeman *et al.*, 2018).

405 Taurine plasma concentrations after supplementation were not measured in most
406 dogs, therefore the effectiveness of supplementation cannot be confirmed. However,
407 in those with taurine concentrations rechecked after supplementation, increased
408 taurine values were recorded. Moreover, in the MUST study (Kittleson *et al.* 1997),
409 all ACS had increased taurine concentrations with similar dose of supplementation
410 as in our study. Furthermore, a study in Newfoundlands showed that taurine
411 supplementation at any dose normalised blood taurine levels and higher doses were
412 associated with increased urinary taurine loss and no changes in plasma or whole
413 blood taurine concentrations (Dukes-McEwan *et al.*, 2001).

414 ~~Moreover~~An additional limitation was that plasma or myocardial carnitine
415 concentrations were not measured and supplementation was started in only one dog
416 making direct comparison with the MUST study impossible.

417 We were unable to determine if the improvements in echocardiographic variables
418 were secondary to the taurine supplementation or due to the other standard cardiac
419 medications; treating dogs with only taurine supplementation would be ethically
420 unacceptable. Moreover, the treatment of dogs was not standardized, although most
421 of the patients were receiving similar medications for CHF. The dogs with normal
422 taurine concentrations (3) were in CHF and this could affect the survival analysis
423 leading to a longer MST for dogs with low taurine concentration (10/13 in CHF). We
424 did not have a MST value for the non-CHF dogs due to the high number of censored
425 cases (1 out of 3).

426 Two dogs were receiving diltiazem to treat supraventricular tachycardias. This could
427 have affected the survival analysis. Tachycardiomyopathy was possible though
428 considered less likely since the arrhythmia was diagnosed after the diagnosis of
429 dilated cardiomyopathy; therefore was believed to be secondary to atrial stretch.”
430 Lastly, one dog had treated hypothyroidism, with historical low serum total thyroxine
431 (T4) concentrations. This dog was not excluded from the study since this condition
432 was considered stable and the dog had been treated with levothyroxine for 4 months
433 prior to inclusion.

434

435 **Conclusions**

436

437 In conclusion, this study has revealed that taurine deficiency is common in ECS
438 affected by DCM; taurine status should be checked in this breed if a diagnosis of
439 DCM is made. Based on the current study, a direct association between these two
440 conditions could not be established but it is suspected. We provided further evidence
441 that ECS have a longer survival time than other breeds with DCM, especially those
442 with taurine deficiency who are supplemented.

443

444 A larger prospective study is needed to confirm the incidence of taurine deficiency in
445 ECS and its association with DCM. The role of supplementing L-carnitine
446 concurrently should also be explored. In particular, including a detailed diet history in
447 prospective assessments will be essential.

448

449 No conflicts of interest have been declared
450

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451

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619

620 **Figures**

621 **Fig. 1** Line chart of the echocardiographic values at admission and at the first
 622 recheck. Only dogs with available echocardiographic values are shown. The dogs
 623 with normal taurine levels are indicated with red dots. The horizontal line is the mean
 624 value.

625 1a) LVESVi: left ventricular end-systolic volume indexed to body surface area. 1b)
 626 LVEDVi: left ventricular end-diastolic volume indexes to body surface area. 1c)
 627 LVIDDN: left ventricular internal dimension in diastole normalized for body weight.
 628 1d) LVIDSN: left ventricular internal diameter in systole normalized for body weight.
 629 1e) EF: ejection fraction. 1f) FS: fractional shortening. 1g) LVIDd: left ventricular
 630 internal dimension in diastole. 1h) EPSS: Mitral M-mode E-point septal separation.

631

632 **Fig 2a** Echocardiographic 2D image of one of the dogs with low taurine
 633 concentration before starting supplementation. Right parasternal long-axis 4-
 634 chambers view showing severe left ventricle dilation. EF: 36%. **Fig 2b**
 635 Echocardiographic M-Mode image of one of the dogs with low taurine concentration
 636 before starting supplementation. Right parasternal short-axis view at the level of the
 637 papillary muscles showing poor systolic function and dilated left ventricle. FS: 11%;
 638 LVESVi: 102.9 mL/m²; LVIDSN: 2.07; LVIDDN: 2.47. **Fig 2c** Echocardiographic 2D
 639 image of one of the dogs with low taurine concentration after starting
 640 supplementation (3 months). Right parasternal long-axis 4-chambers view showing
 641 less severe left ventricle dilation. EF: 47%. **Fig 2d** Echocardiographic M-Mode image
 642 of one of the dogs with low taurine concentration after starting supplementation (3
 643 months). Right parasternal short-axis view at the level of the papillary muscles
 644 showing improved systolic function and left ventricular dimensions. FS: 7%; LVESVi:
 645 64.2 mL/m²; LVIDSN: 1.07; LVIDDN: 1.93.

646 Abbreviations: EF: ejection fraction. FS: fractional shortening. LVESVi: left
 647 ventricular end-systolic volume indexed to body surface area. LVIDSN: left
 648 ventricular internal diameter in systole normalized for body weight. LVIDDN: left
 649 ventricular internal diameter in diastole normalized for body weight.

650

651 **Fig. 3a** Graphic representation of the left ventricular end-systolic volume indexed to
 652 body surface area of all dogs with echocardiographic follow-up values. **Fig. 3b**
 653 Graphic representation of the left ventricular internal dimension in systole normalized
 654 for body weight of all dogs with echocardiographic follow-up values.

655 Red dots indicate dogs with normal taurine levels. Each dot indicates an
 656 echocardiographic examination.

657 Abbreviations: LVESVi: left ventricular end-systolic volume indexed to body surface
 658 area. LVIDSN: left ventricular internal diameter in systole normalized for body
 659 weight.

660

661 **Fig. 4** Kaplan Meier survival curve of the entire population of dogs included in the
 662 study.

663

664

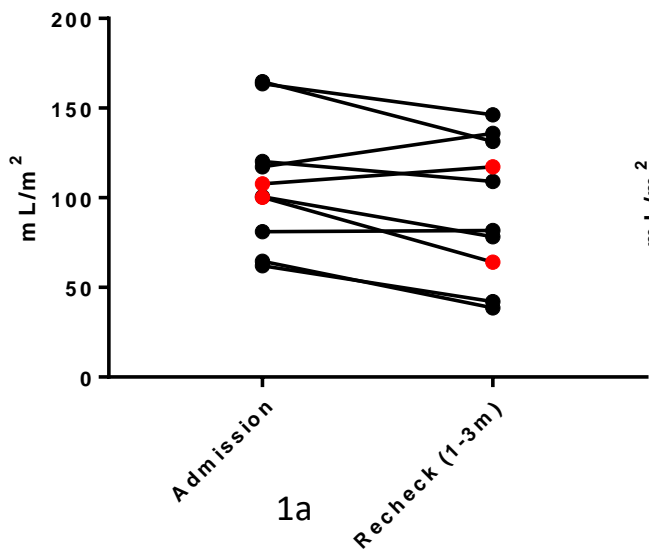
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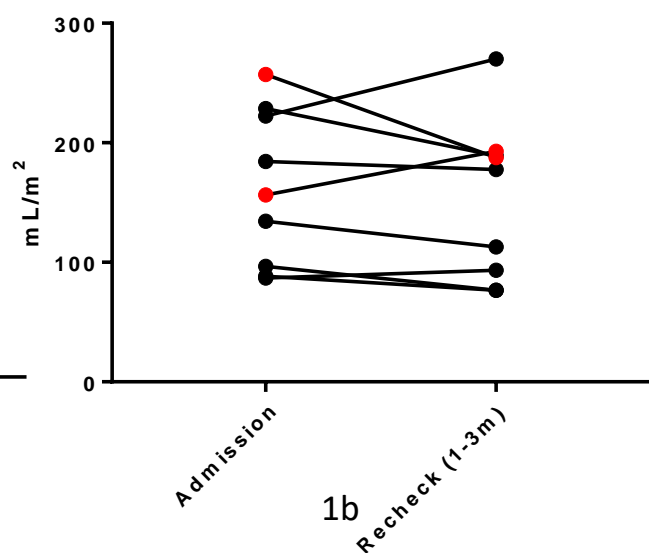
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LVESVi



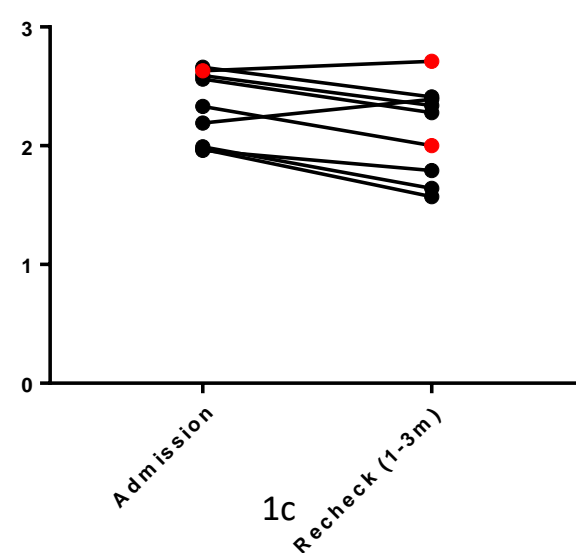
1a

LVEDVi



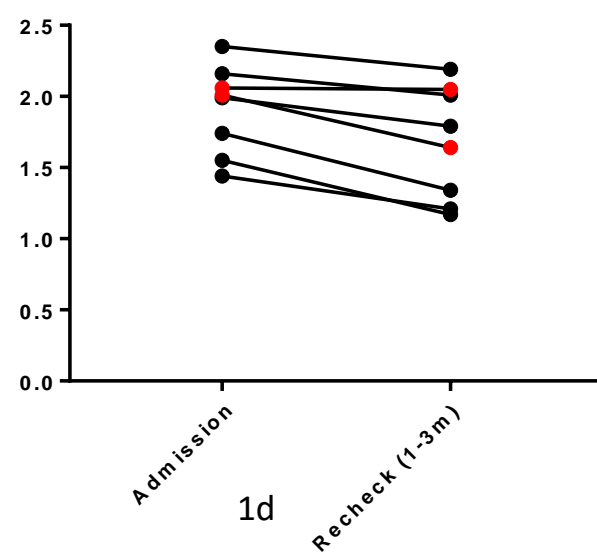
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LVIDDn



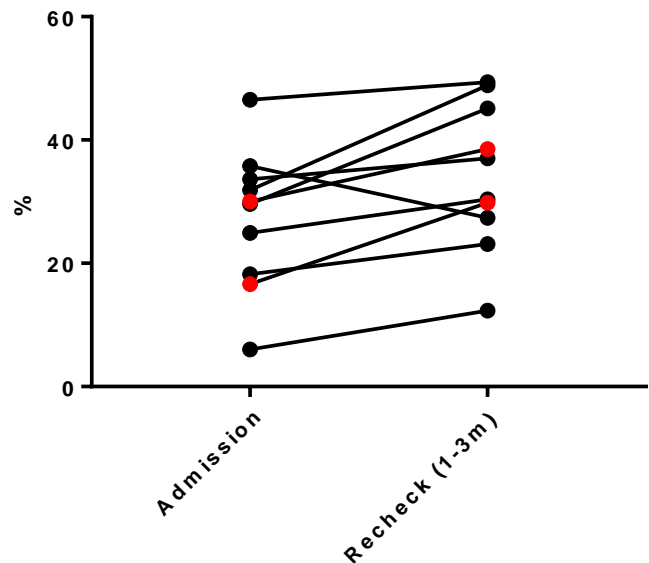
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LVIDSn



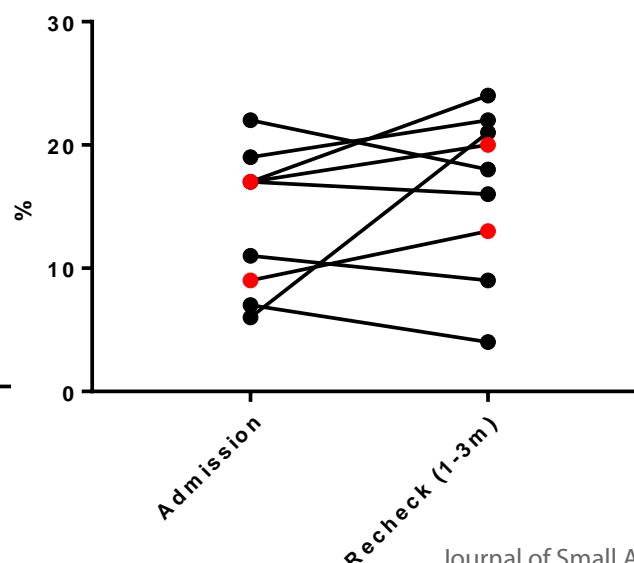
1d

EF



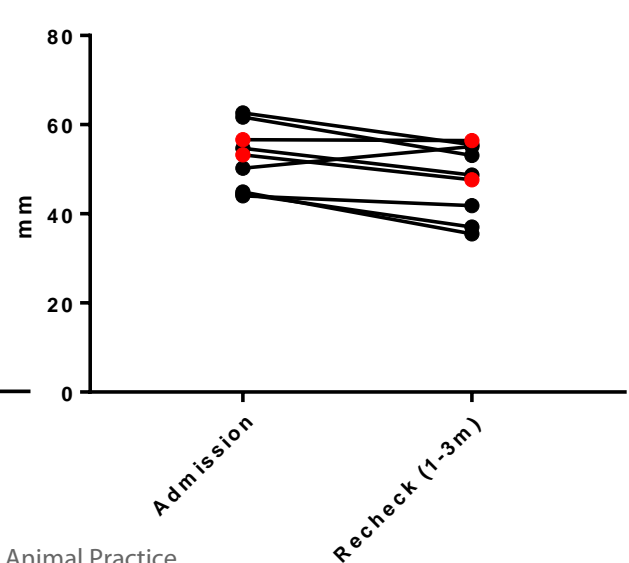
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FS



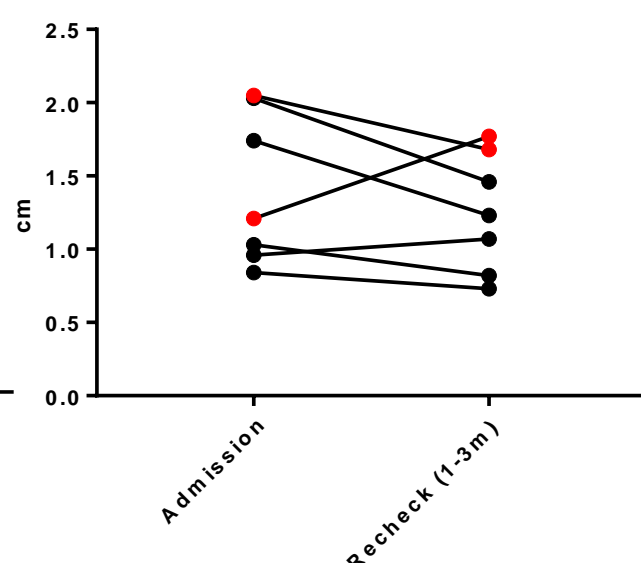
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LVIDd



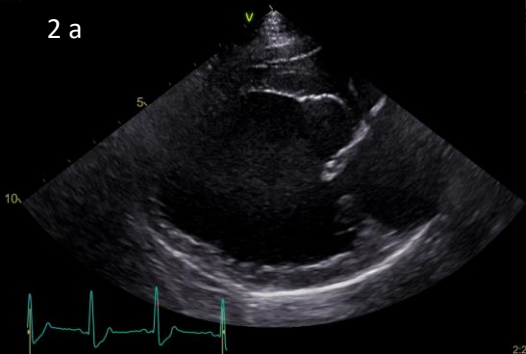
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EPSS

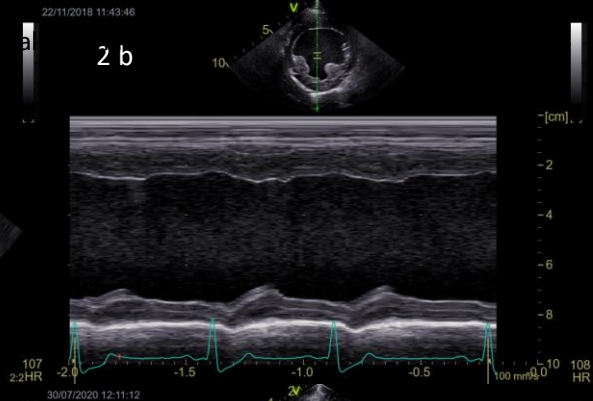


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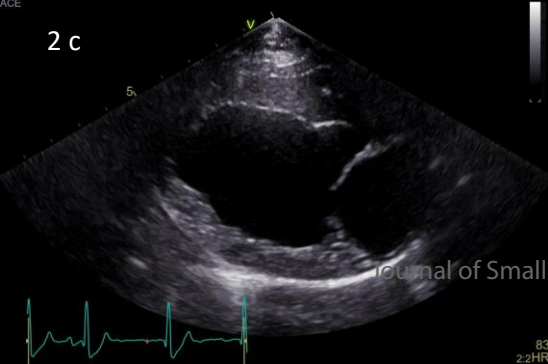
2 a



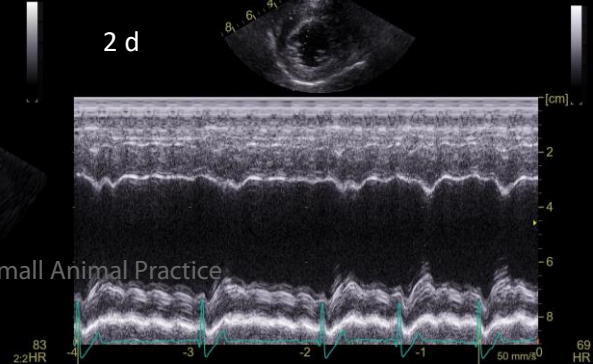
2 b



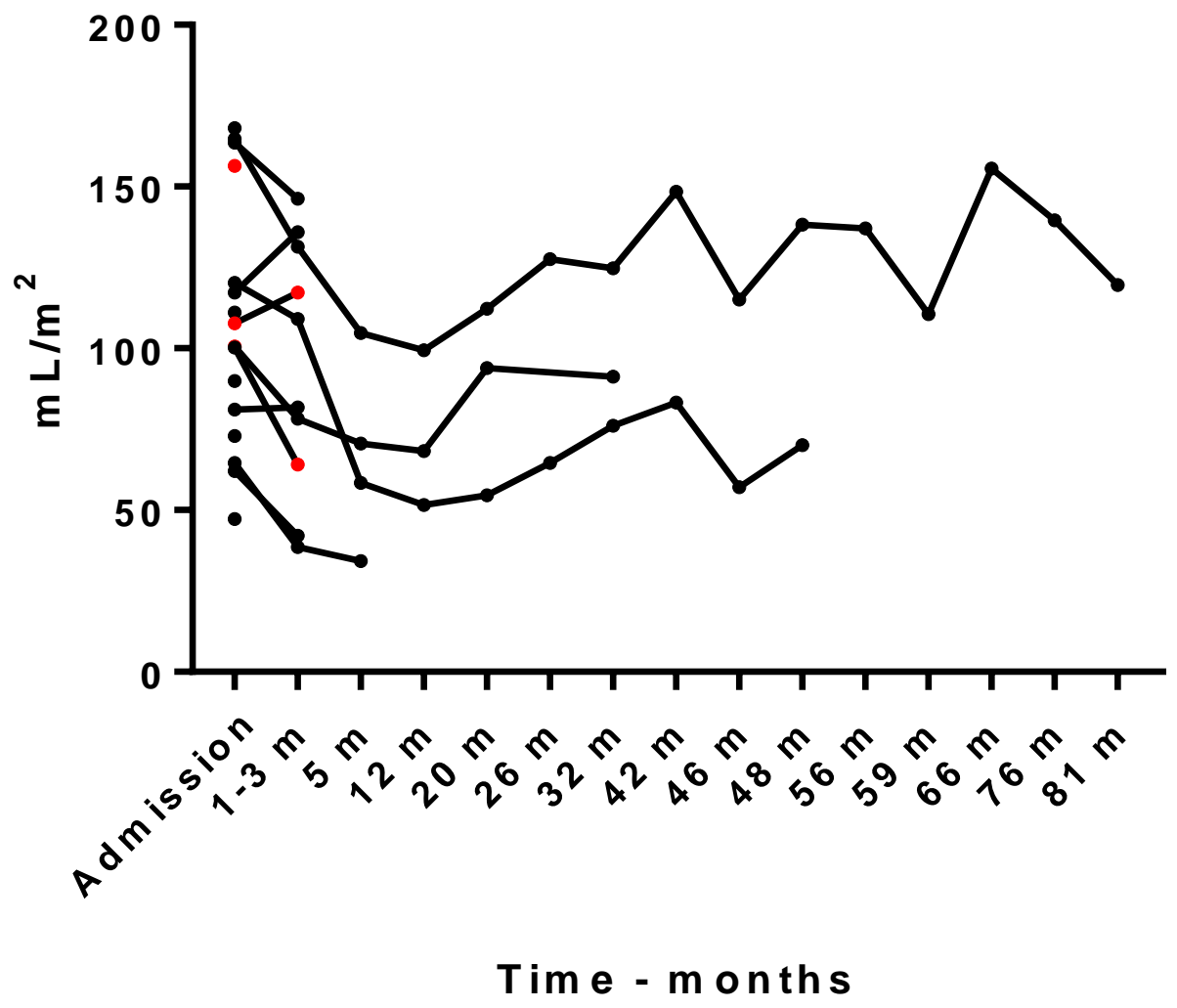
2 c



2 d

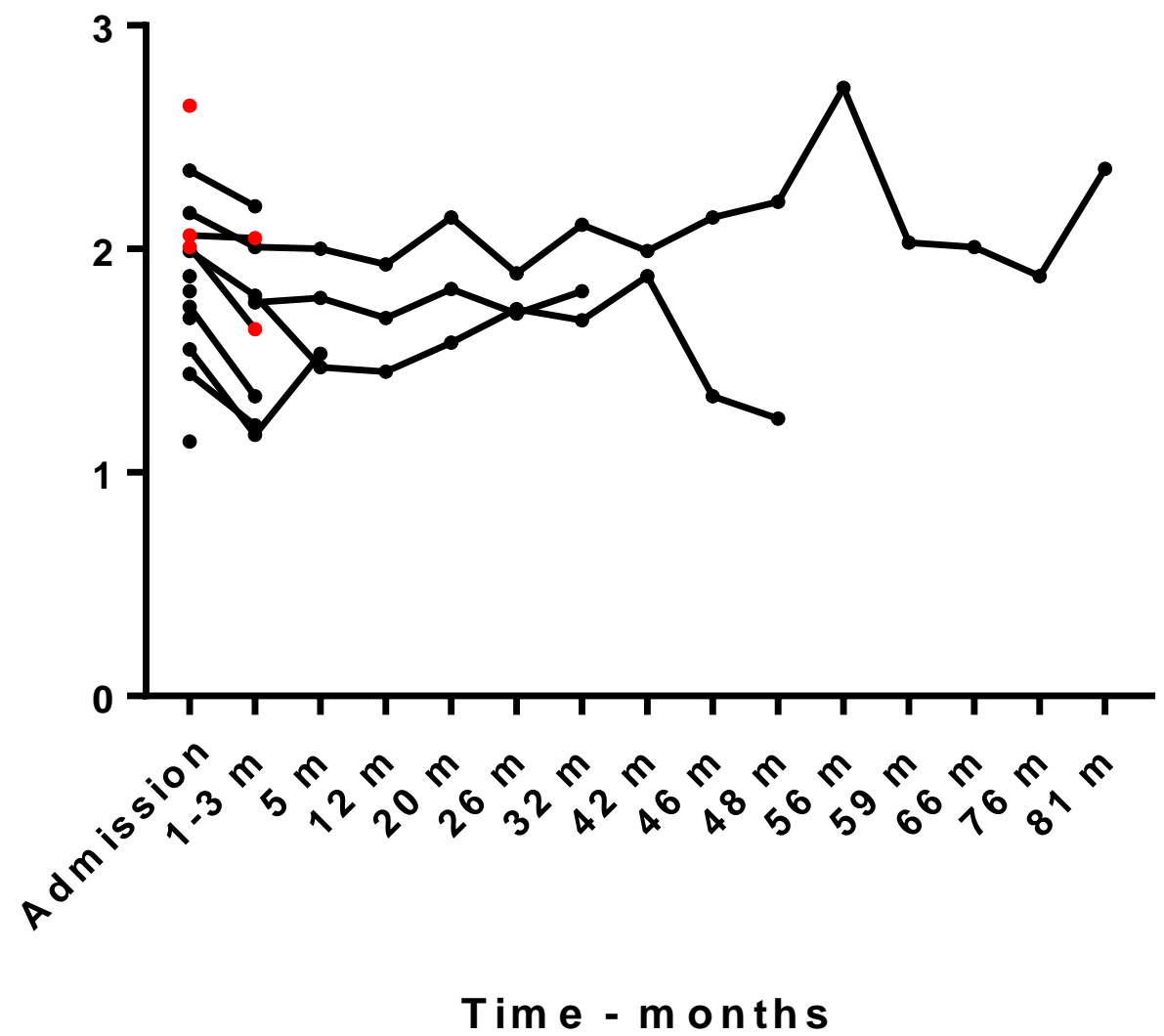


LVESVi



3a

LVIDSN



3b

Survival of all dogs

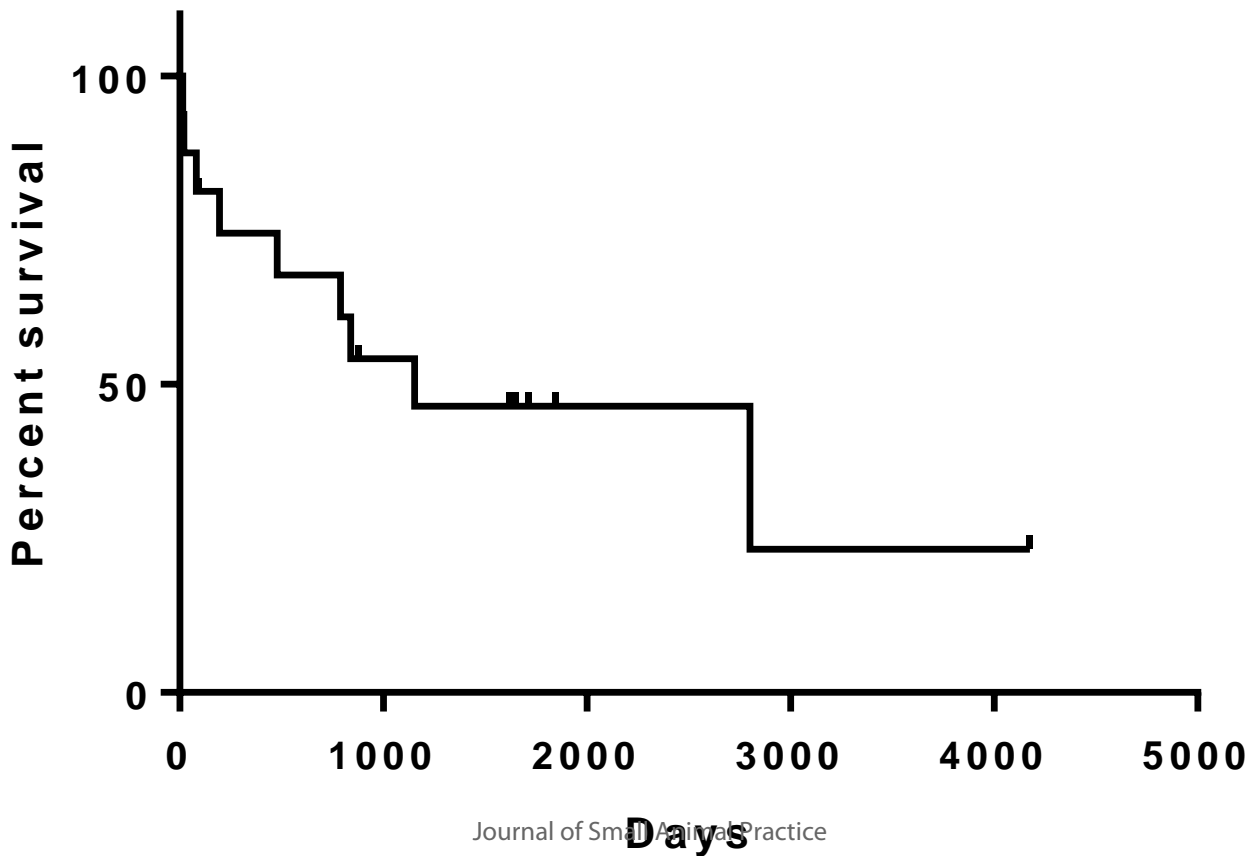


Table 1. Signalment, taurine concentrations, medications received, [outcome and survival time](#) of all dogs included in the study.

	Group	Age	Sex	Weight	Taurine plasma concentration (ref. 50-180 umol/L)	Taurine plasma concentration 6 months after supplementation	Pimobendan (mg/kg/day)	Furosemide (mg/kg/day)	Spironolactone (mg/kg/day)	Benzazepril (mg/kg/day)	Taurine supplementation (mg/kg/day)	Additional medications	First recheck interval (days)	Outcome	Survival time (days)
Dog 1	LTC	1	MN	17.5	22					0.6	66		NA	Lost to follow-up	NA
Dog 2	LTC, CHF	9	MN	16.7	2		0.6	7.5	1	0.3	30		NA	Lost to follow-up	NA
Dog 3	LTC, CHF	7	FN	17	6	200	1	7.5	2.5	0.33	116		90	Died of cardiac death	790
Dog 4	LTC, CHF	4	M	16	26		0.6	1.2		0.33	66	Carnitine	NA	Died of cardiac death	1155
Dog 5	LTC, CHF	8	FN	15.4	39		0.6	3.6		0.3	122	Diltiazem Levothyroxine	90	Alive	1550
Dog 6	LTC, CHF	9	MN	14.7	9		0.6	9.9	2.5	0.3	17	Hydrochlorothiazide Amiloride	7	Lost to follow-up	NA
Dog 7	LTC, CHF	3	FE	9.5	29		1	6	1	0.5	50		NA	Died of cardiac death	20
Dog 8	LTC, CHF	7	FN	15	9		0.6	6.6	2.2	0.33	33	Amlodipine	30	Lost to follow-up	NA
Dog 9	LTC, CHF	4	MN	20.8	5		0.5	6	2	0.25	50		30	Alive	2430

Dog 10	LTC	10	M	15	27		0.6				66		30	Died of cardiac death	840
Dog 11	LTC, CHF	8	FN	11.7	19		0.5	9	4	0.5	150	Clopidogrel	60	Died of cardiac death	195
Dog 12	LTC	9	ME	14.7	19		0.3				66	Diltiazem Clopidogrel	NA	Died of cardiac death	83
Dog 13	LTC, CHF	2	ME	18.9	15	279	0.4	6	2.5	0.3	50		90	Died of cardiac death	2800
Dog 14	NTC, CHF	11	MN	13.5	75		0.8	9	1.2	0.4	80	Hydrochlorothiazide Amiloride	30	Died of cardiac death	478
Dog 15	NTC, CHF	9	MN	13.6	194		0.5	6	1.3	0.33		Clopidogrel Sildenafil Kaminox Doxycycline	90	Died of cardiac death	14
Dog 16	NTC, CHF	7	ME	16.5	81		0.5	5	2.3	0.3			90	Alive	910

Dog n° 14 had taurine concentrations close to the lower reference interval and was supplemented. Dog n° 4 received carnitine despite lack of concentration measurements. Abbreviations: ME: male entire. MN: male neutered. FE: female entire. FN: female neutered. LTC: low taurine concentration. NTC: normal-aurine concentration. CHF: congestive heart failure.

Table 2. Mean echocardiographic values of the dogs included in the study at admission and at the first recheck after admission; subdivided in all population, LTC and NTC.

<u>ALL POPULATION</u>	Variables at admission: mean (\pm standard deviation; SD)	First recheck after admission: mean (\pm SD)
LVIDd (mm)	51.55 (\pm 9.6)	49.92 (\pm 10.6)
LVIDDN	2.32 (\pm 0.45)	2.26 (\pm 0.53)
LVIDSN	1.88 (\pm 0.39)	1.68 (\pm 0.37)
LVESVi (mLs/m ²)	107.9 (\pm 38.8)	94.4 (\pm 39.0)
LVEDVi (mLs/m ²)	153.9 (\pm 60.78)	152.9 (\pm 66.38)
Ejection fraction (%)	27.4 (\pm 10.6)	34.1 (\pm 11.89)
Fractional shortening (%)	14.89 (\pm 5.94)	16.62 (\pm 7.43)
EPSS (mm)	15.5 (\pm 5.1)	14.5 (\pm 5.0)
<u>LTC</u>		
LVIDd (mm)	49.69 (\pm 8.7)	46.67 (\pm 6.5)
LVIDDN	2.22 (\pm 0.38)	2.06 (\pm 0.37)
LVIDSN	1.77 (\pm 0.35)	1.63 (\pm 0.40)
LVESVi (mLs/m ²)	104.8 (\pm 40.8)	95.4 (\pm 41.8)
LVEDVi (mLs/m ²)	148 (\pm 63.1)	140 (\pm 69.1)
Ejection fraction (%)	28.1 (\pm 11.4)	34.1 (\pm 13.2)
Fractional shortening (%)	14.87 % (\pm 6.37)	16.28 (\pm 7.31)
EPSS (mm)	14.4 (\pm 5.0)	11.8 (\pm 4.5)

<u>NTC (individual values)</u>		
LVIDd (mm)	56.6 / 68.8 / 53.2	56.4 / 47.6
LVIDDN	2.63 / 3.19 / 2.33	2.71 / 2
LVIDSN	2.06 / 2.64 / 2.01	2.05 / 1.64
LVESVi (mLs/m ²)	107.8 / 156.4 / 100.2	117.3 / 64.1
LVEDVi (mLs/m ²)	156.4 / 215.7	192.9
Ejection fraction (%)	30 / 26.8 / 16.6	38.5 / 29.8
Fractional shortening (%)	17 / 13 / 9	20 / 13
EPSS (mm)	2.05 / 2.07 / 1.21	1.68 / 1.77

At the recheck 5 dogs in the LTC did not have values available.

Abbreviations: LTC: low taurine concentration. NTC: normal-aurine concentration. LVIDd: left ventricular internal diameter in diastole. LVIDDN: left ventricular internal diameter in diastole normalized for body weight. LVIDSN: left ventricular internal diameter in systole normalized for body weight. LVESVi: left ventricular end-systolic volume indexed to body surface area. LVEDVi: left ventricular end-diastolic volume indexed to body surface area. EPSS: Mitral M-mode E-point septal separation. NA not applicable.