Low plasma taurine levels in English cocker spaniels diagnosed with dilated cardiomyopathy

M. Basili †*, B. Pedro ‡, H. Hodgkiss-Geere †, X. Navarro-Cubas †§, N. Graeff † and J. Dukes-McEwan †

*Cardiology Service, Small Animal Teaching Hospital, Institute of Infection, Veterinary and Ecological Science, University of Liverpool, Neston, Chester, CH64 7TE, UK
†Cardiology Service, Willows Veterinary Centre and Referral Service, Shirley, Solihull B90 4NH, UK
‡Cardiology Service, Southfields Veterinary Specialists, Basildon, Essex SS15 6TP, UK
1Corresponding author email: mattia.basili@liverpool.ac.uk

OBJECTIVES: The aims of this study were to evaluate taurine levels in English cocker spaniels with dilated cardiomyopathy and assess their survival time and natural progression of their disease.

MATERIALS AND METHODS: Retrospective comparison of English cocker spaniels with dilated cardiomyopathy phenotype with and without taurine deficiency at the cardiology department of a UK academic referral centre between 2008 and 2018.

RESULTS: Taurine plasma concentration was available in 16 English cocker spaniels with dilated cardiomyopathy phenotype; 13 of 16 had congestive heart failure and three of 16 did not. Taurine concentration was low (<50 μmol/L) in 13 of 16 and normal in three of 16. Deficient dogs received taurine supplementation in addition to conventional cardiac medications. Eight dogs were still alive at the end of this study and eight were dead. MST for all dogs included in the study was 2800 days. Left ventricular systolic function improved and left ventricular dimensions reduced in English cocker spaniels with taurine deficiency following taurine supplementation and conventional cardiac therapy, although similar results were observed in English cocker spaniels with normal taurine concentration on cardiac therapy alone.

CLINICAL SIGNIFICANCE: Based on laboratory reference intervals, low taurine concentrations were common in English cocker spaniels with dilated cardiomyopathy, showing a possible association between dilated cardiomyopathy in English cocker spaniels and taurine deficiency; supplementation with taurine was not curative.

INTRODUCTION

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

Primary (idiopathic) DCM has been documented in a number of breeds including English cocker spaniel (ECS) (Good-
Taurine deficiency and DCM in cocker spaniels

ing et al. 1982, 1986, Thomas 1987, Tidholm et al. 1997). In a large UK survey of dogs presenting with DCM, ECS was the fourth most common breed affected, with 30 of 369 cases and was reported to have longer survival times compared with other breeds Martin et al. 2009).

The DCM phenotype may be a consequence of heritable genetic mutations, viral infections, immune-mediated disorders, arrhythmias, toxins, and nutritional deficiencies (Van Vleet & Ferrans 1986; Shinbane et al. 1997; Backus et al. 2006). Due to familial disease, a genetic basis is suspected in some breeds and already documented in others, as recently reviewed by Dutton & López-Alvarez (2018). Prior to making the diagnosis of DCM, other conditions that may result in similar echocardiographic changes must be actively excluded.

Taurine deficiency has been implicated as a nutritional cause of a DCM phenotype. This was initially reported in a group of cats affected by DCM, where the phenotype completely reversed with taurine supplementation; before this discovery, the prognosis for cats with DCM caused by taurine deficiency was grave (Pion et al. 1987). Later, American cocker spaniels (ACSs) with low taurine concentrations were also reported to at least partially reverse their DCM phenotype after both taurine and l-carnitine supplementation (Kittleson et al. 1997). Other studies reported similar findings in this and other breeds such as Golden Retrievers (Kramer et al. 1995, Gavaghan & Kittleson 1997, Kaplan et al. 2018, Ontiveros et al. 2020).

English cocker spaniels were imported into the USA in the 19th century: ACSs were developed and eventually recognised as a different breed in 1936 (Fogle 1996). Therefore, there is likely to be a genetic relationship between the ACS studied by Kittleson et al. (1997) and the ECS population. To the authors’ knowledge, no studies have been reported investigating taurine deficiency in ECS with DCM.

The main aim of this study was to investigate the possible association between taurine deficiency and DCM in ECS in the UK. The hypothesis was that ECS with a diagnosis of DCM could also have low taurine levels, similar to ACS. Additional aims of this study were to investigate the response to taurine supplementation in deficient ECS and document the progression of DCM and survival times in this breed.

**MATERIALS AND METHODS**

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

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

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

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

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

For taurine analysis, heparinised plasma samples were submitted to IDEXX (Referral assay via IDEXX Laboratories, Wetherby, United Kingdom). Samples were centrifuged and plasma separated within 30 minutes of the blood sample being taken. Taurine deficiency was defined as concentrations <50 μmol/L, based on the laboratory’s reference range interval (50–180 μmol/L); these were extrapolated from the MUST study (Kittleson et al. 1997) and were also confirmed in other studies that included various breeds (Kramer et al. 1995; Delaney et al. 2003; Törres et al. 2003).

Doppler Echocardiographic examinations were carried out using a GE Vivid 7 (Buckinghamshire, UK) machine, using a 7S or M4S transducer. The dogs were in lateral recumbency on a purpose-designed table to allow imaging via the dependent thoracic wall. Studies have been performed by either a cardiology diplomat or a cardiology resident under the direct supervision of a diplomate. Two dimensional (2D) and M-mode images were acquired, recorded and measured according to standard protocols (Sahn et al. 1978, Thomas et al. 1994, Boon 1998). Data from the M-mode studies retrieved included left ventricular internal dimensions both in diastole (LVIDd) and systole (LVIDs); fractional shortening (FS) was calculated. The M-mode LV diameters were normalised for bodyweight by allometric scaling in diastole (LVIDDD) and systole (LVIDSN) Cornell et al. 2004). The mitral E point to septal separation (EPSS) measurement from mitral valve M-mode was also recorded. From the 2D right parasternal long axis 4 chamber view optimising the left ventricular length and area, Simpson's method of discs was used to determine LV end-diastolic and end-systolic volumes. Ejection fraction (EF) and sphericity index were calculated (Dukes-McEwan et al. 2003). The end-systolic and end-diastolic volumes indexed to body surface area (BSA) were also calculated (LVESVi and LVEDVi, respectively). The BSA was calculated using the standard formula (Ford & Mazzaferrro 2011). Maximal left atrial diameter, measured at the end of ventricular systole from a right parasternal long-axis 4 chamber view and the short axis ratio of the left atrium to aortic diameters, measured at the end of diastole, were recorded (Chetboul & Tissier 2012). Colour flow and
Spectral Doppler were used to exclude other significant cardiac diseases. Mitral regurgitation was accepted provided it was a central jet implying origin due predominantly to stretch of the mitral annulus, rather than primary mitral valve disease (myxomatous or dysplastic); dogs with markedly thickened or prolapsing mitral leaflets were not included. Colour flow and spectral Doppler transvalvular flows were documented, but not analysed further for purposes of this study.

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

Congestive heart failure was defined as left-sided if there were compatible radiographic findings, when available; in the absence of radiographs, echocardiographic signs of increased left filling pressures (Schober et al. 2010) in association with clinical signs and response to furosemide administration were considered supportive of CHF. Radiographs had been reviewed and reported by diagnostic imaging diplomates or diagnostic imaging residents working under supervision of a diplomate.

If dogs had plasma taurine level < 50 μmol/L, supplementation with taurine was commenced. Dogs with CHF or with pre-clinical DCM were treated according to the individual clinician and owner preference. Drugs used and their doses were recorded.

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

**Statistical analysis**

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

Survival time was evaluated for dogs with low and normal taurine levels. A Kaplan–Meier curve was constructed. Dogs were censored due to worsening of their cardiac disease (Table 1). Four dogs died of other non-cardiac diseases. Mitral regurgitation was accepted provided it was a central jet implying origin due predominantly to stretch of the mitral annulus, rather than primary mitral valve disease (myxomatous or dysplastic); dogs with markedly thickened or prolapsing mitral leaflets were not included. Colour flow and spectral Doppler transvalvular flows were documented, but not analysed further for purposes of this study.

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**RESULTS**

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

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

Sixteen dogs met the inclusion criteria: 13 of 16 had low plasma taurine concentration. In the dogs with low plasma taurine, the mean taurine concentration was 17.46 ± 11.03 μmol/L. Three dogs had normal taurine concentrations (75, 81 and 194 μmol/L). Thirteen dogs were in congestive heart failure. The three of 16 dogs that did not have CHF all had low taurine concentrations.

The mean age of the dogs included in the study was 6.75 ± 3.02 years, the mean bodyweight was 15.3 ± 2.7 kg. There were 11 males and five females included. There were eight males (four neutered) and five females (four neutered) with low taurine levels. All dogs with normal taurine levels were males (two neutered). Signalment, taurine concentrations, CHF status and medications including taurine supplementation and outcome at the time of writing are reported for each individual dog in Table 1.

Taurine supplementation was started in all dogs with low taurine concentration at a dose of 67.8 ± 38.9 mg/kg/day. Eleven dogs did not have taurine levels rechecked, though the two dogs with low taurine levels that did have further measurements 6 months later showed values of 200 and 279 μmol/L (ref. 50 to 180). All dogs received one or more cardiac medications; eight dogs were receiving other medications or supplements (Table 1).

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

Echocardiographic variables at admission and at follow-up (median 30 days; range 7 to 90) were reported (Table 2). Serial echocardiographic studies were available for 10 of 16 dogs. Comparison between echocardiographic variables at baseline and at the first follow-up is shown in Figure 1. Figure 2 shows echocardiographic images of one of the dogs with low taurine concentration with dilated left ventricle and poor systolic function before (Fig 2A, B) and after (Fig 2C, D) taurine supplementation; there is improvement of left ventricular dimensions and systolic function at the recheck although statistical comparison was not performed. In all dogs included in the study, there was a subjective improvement between admission and first re-check values of LVEF, LVIDS, LVIDD and EF. The dogs with low taurine levels showed a subjective improvement between admission and re-check values of LVIDS and LVIDD, but not in LVEF and EF. Again, all the above values were not statistically compared due to low numbers and to avoid “testing against baseline”. For the dogs that underwent serial echocardiographic examinations, graphical representation of LVEF and LVIDS values over time is shown in Fig 3A, B (Fig 3A, B).

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

The median survival time (MST) for all dogs included in the study was 1155 days (195–2800) (Fig 4). Dogs with low taurine levels had a MST of 2800 days (790 – upper limit not calculable), whereas those with normal levels had a survival time of 14, 90 and 478 days. The 13 dogs with CHF (10 with low taurine levels...
### Table 1. Signalment, taurine concentrations, medications received, outcome and survival time of all dogs included in the study

| Group | Age | Sex | Weight (kg) | Taurine plasma concentration (ref. 50–180 umol/L) | Pimobendan (mg/kg/day) | Furosemide (mg/kg/day) | Spironolactone (mg/kg/day) | Benazepril (mg/kg/day) | Taurine supplementation (mg/kg/day) | Additional medications | First recheck interval (days) | Outcome | Survival time (days) |
|-------|-----|-----|-------------|-----------------------------------------------|------------------------|----------------------|--------------------------|--------------------------|-----------------------------------|------------------------|--------------------------|----------|---------------------|
| Dog 1 | LTC | MN  | 17.5        | 22                                            | 0.6                    | 66                   | NA                       | NA                       | NA                                | Lost to follow-up            | 66                       | NA        | NA                  |
| Dog 2 | LTC, CHF | 9 MN | 16.7        | 2                                             | 0.6                    | 7.5                  | 1                        | 0.3                      | 30                                | Lost to follow-up            | 66                       | NA        | NA                  |
| Dog 3 | LTC, OHF | 7 FN | 17          | 6                                             | 1                      | 7.5                  | 2.5                      | 0.33                     | 116                               | Died of cardiac death         | 90                       | NA        | 790                 |
| Dog 4 | LTC, OHF | 4 M  | 16          | 26                                            | 0.6                    | 1.2                  | 0.33                     | 66                       | NA                                | Died of cardiac death         | 90                       | NA        | 1155                |
| Dog 5 | LTC, OHF | 8 FN | 15.4        | 39                                            | 0.6                    | 3.6                  | 0.3                      | 122                      | NA                                | Live                   | 1550                   | 3000                |
| Dog 6 | LTC, OHF | 9 MN | 14.7        | 9                                             | 0.6                    | 9.9                  | 2.5                      | 0.3                      | 17                                | Died of cardiac death         | 7                       | NA        | 150                 |
| Dog 7 | LTC, OHF | 3 FE | 9.5         | 29                                            | 1                      | 6                    | 1                        | 0.5                      | 50                                | Died of cardiac death         | 90                       | NA        | 20                  |
| Dog 8 | LTC, OHF | 7 FN | 15          | 9                                             | 0.6                    | 6.6                  | 2.2                      | 0.33                     | 33                                | Died of cardiac death         | 30                      | NA        | 30                  |
| Dog 9 | LTC, OHF | 4 MN | 20.8        | 5                                             | 0.6                    | 6                    | 2                        | 0.25                     | 50                                | Died of cardiac death         | 30                      | NA        | 2430                |
| Dog 10 | LTC, OHF | 10 M | 15          | 27                                            | 0.5                    | 6                    | 2                        | 0.25                     | 50                                | Died of cardiac death         | 30                      | NA        | 840                 |
| Dog 11 | LTC, OHF | 8 FN | 11.7        | 19                                            | 0.5                    | 9                    | 4                        | 0.5                      | 150                               | Died of cardiac death         | 60                      | NA        | 195                 |
| Dog 12 | LTC | 9 ME | 14.7        | 19                                            | 0.5                    | 9                    | 4                        | 0.5                      | 150                               | Died of cardiac death         | 60                      | NA        | 83                  |
| Dog 13 | LTC, OHF | 2 ME | 18.9        | 15                                            | 0.4                    | 6                    | 2.5                      | 0.3                      | 50                                | Died of cardiac death         | 90                      | NA        | 2800                |
| Dog 14 | NTC, CHF | 11 MN | 13.5        | 75                                            | 0.8                    | 9                    | 1.2                      | 0.4                      | 80                                | Died of cardiac death         | 30                      | NA        | 478                 |
| Dog 15 | NTC, CHF | 9 MN | 13.6        | 194                                           | 0.5                    | 6                    | 1.3                      | 0.33                     | 90                                | Died of cardiac death         | 90                      | NA        | 14                  |
| Dog 16 | NTC, CHF | 7 ME | 16.5        | 81                                            | 0.5                    | 5                    | 2.3                      | 0.3                      | 90                                | Alive                   | 910                     | 910                  |

LTC: Low taurine concentration, MN Male neutered, CHF: Congestive heart failure, FN Female neutered, FE Female entire, ME Male entire, NTC Normal taurine concentration, NA Not applicable. 
Dog 14 had taurine concentrations close to the lower reference interval and was supplemented. Dog 4 received carnitine despite lack of concentration measurements.
We did not measure the whole blood taurine concentrations and these have been reported to be substantially higher than plasma taurine concentrations. Whole blood taurine concentration may be superior, if available, as it more closely reflects muscle taurine concentration and therefore overall taurine status, whereas plasma taurine may reflect fasting or post-prandial status (Delaney et al. 2003). For this study, only plasma taurine concentrations could be assayed and no records were made of when each dog's last meal had been taken before sampling.

As mentioned above, no statistical analysis was performed between admission and re-check echocardiography values in order to avoid “testing against baseline”, therefore only subjective or visual assessments could be made; however, it is interesting to notice changes that we recorded in our dogs during the study period. As Figs 1A–H and 3A, B show, at the first follow-up echocardiography values showed reduction in LV diameter and volumes (LVIdd, LVESVi, LVIDDN, LVIDSN) with improved systolic function (EF, LVESVi) if the whole population was considered. However, those with low taurine levels at the re-check had an improvement in LVIdd, LVIDDN and LVIDSN but not in LVESVi and EF. In line with our data, Kittleson et al. (1997) reported that ACS with DCM and low taurine concentrations showed improved systolic function after supplementation. Taurine supplementation may improve systolic function, even in the absence of a taurine deficient state as shown in a study conducted in people with chronic CHF where taurine supplementation was given for 6 weeks and a substantial improvement in systolic function was reported (Azuma et al. 1992). Therefore, it is possible that taurine supplementation at pharmacological doses could have played a role in the reduction of the LV chamber dimensions and improvement in systolic function in our population of ECS, even if low-taurine status was not associated with their DCM. Since all ECSs also received conventional cardiac therapy, it is not possible to separate the effects of this medications from taurine supplementation in ECS with low taurine concentrations. Diuretics reduce preload, which will reduce LV size (showed by a reduction in values of LVIdd), as well as resolving fluid retention associated with CHF due to both systolic dysfunction and RAAS activation. It is also well documented that pimobendan reduces ventricular size in both CHF and preclinical DCM patients as well as dogs with mitral valve myxomatous disease (Summerfield et al. 2012, Haggström et al. 2013, Boswood et al. 2016).

A relationship between taurine deficiency and DCM phenotype in ACS was initially reported by Kramer et al. (1995). A few years later, in the multicentred spaniel trial (MUST) study, Kittleson et al. (1997) showed an improved systolic function in the breed following supplementation with both taurine and L-carnitine. Unfortunately, the concurrent use of both supplements makes it unclear whether the response observed was due to the concurrent L-carnitine supplementation. In our study, myocardial L-carnitine levels were not assessed, as myocardial biopsies are required for diagnosing carnitine deficiency (Meurs 2004) and L-carnitine was only supplemented in one dog (dog 4 in Table 1), who died a cardiac death 115 days after diagnosis without a follow-up echocardiography. It is therefore possible that different results may have been achieved if L-carnitine was also

### DISCUSSION

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

In dogs with serial echocardiographic data, we did not carry out any statistical analysis in view of small numbers in this descriptive study. However, data suggest that taurine supplementation might not be curative and taurine deficiency may not be the sole cause of DCM phenotype in this breed. This has also been seen in other breeds such as ACS, Golden retrievers, Newfoundlands and Irish Wolfhounds (Kittleson et al. 1997, Fascetti et al. 2003, Alroy et al. 2005, Bélinger et al. 2005, Backus et al. 2006, Vollmar et al. 2013). In contrast, cats with taurine-deficient DCM have a reversible cardiomyopathy with taurine supplementation (Pion et al. 1987).
Two dogs with low taurine levels and one with normal taurine levels received clopidogrel due to the presence of left atrial spontaneous echocontrast. This can also be associated with low velocity blood flow or inflammatory disease and both conditions can lead to thrombus formation. (Spence et al. 2019).

In this study, ECS affected by DCM and CHF had a MST of 1155 days, which is longer than the survival time associated with DCM and CHF reported in other breeds. A survival time of 27 days was reported in 189 dogs of various breeds with DCM and CHF, whereas a MST of 65 days was found in a group of 37 dogs affected by DCM; in both these studies, dogs did not receive pimobendan (Monnet et al. 1995, Tidholm et al. 1997). More recent data showed a MST of 133 days in 369 dogs of various breeds with DCM (74% in CHF at presentation) (Martin et al. 2009). Dobermanns in CHF were also shown to have a short MST of 50.67 days that increased to 329 days with pimobendan therapy (Luis Fuentes et al. 2002). Dobermanns with preclinical DCM at presentation had times to primary endpoint (sudden death or CHF) of 441 days, which was shown to increase to 718 days in dogs receiving pimobendan (Summerfield et al. 2012). American cocker spaniels with DCM and low-taurine in the MUST study (Kittleson et al. 1997) had a longer MST (849 days) than that reported in previous studies, but still shorter than our ECS. Data from an unpublished study state a MST of ECS with DCM of 750 days (Wotton 1998); however, taurine levels were not measured in these dogs, nor was it supplemented. In the study by Luis Fuentes et al. (2002), ECS receiv-
ing placebo or pimobendan had a MST of 537 and 1037 days, respectively, showing considerably longer survival time compared to other breeds, which is supported by the results presented here. The most recent comparison of different breeds with DCM showed ECS with DCM to have a MST of 511 days, the longest amongst all the breeds in the study (Pedro et al. 2011). It can be appreciated from these studies that the MST may be longer in ECS, compared with other breeds with DCM.
Histopathology was not performed in any of the cases included in the study, therefore, the diagnosis was based on echocardiographic findings. We also did not obtain pedigree information from these dogs, so we were not able to investigate for familial DCM, or possible inherited basis for the taurine deficiency. This should be addressed in future prospective studies.

Dogs were classified as taurine deficient based on the laboratory reference interval but breed specific reference range is currently not available. Ideally, taurine concentration should have been tested in a control group of ECS without DCM since it is possible that this breed has different basal plasma taurine levels as demonstrated in Golden Retrievers (Ontiveros et al. 2020). Also, whole blood taurine concentrations were not measured in this study.

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

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

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

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

Two dogs were receiving diltiazem to treat supraventricular tachycardias. This could have affected the survival analysis. Tachycardiomypathy was possible though considered less likely since the arrhythmia was diagnosed after the diagnosis of dilated cardiomyopathy; therefore was believed to be secondary to atrial stretch.

Lastly, one dog had treated hypothyroidism, with historical low serum total thyroxine (T4) concentrations. This dog was not excluded from the study since this condition was considered stable and the dog had been treated with levothyroxine for 4 months before inclusion.

In conclusion, this study has revealed that taurine deficiency is common in ECS affected by DCM; taurine status should be addressed in future prospective studies.

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

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

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

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

We did not compare echocardiographic values between baseline and recheck to avoid “testing against baseline”, therefore, the above results should be considered as subjective based on visual assessments of the graphs. The echocardiographic examinations were performed by different operators and inter-operator and inter-observer variabilities were not assessed as part of this study. However, all echocardiographers had undergone similar training and followed similar acquisition and measurement protocols.
checked in this breed if a diagnosis of DCM is made. Based on the current study, a direct association between these two conditions could not be established but it is suspected. We provided further evidence that ECSs have a longer survival time than other breeds with DCM, especially those with taurine deficiency who are supplemented.

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

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Conflict of interest

No conflicts of interest have been declared.

Ethical Approval

The study had institutional ethical approval (VREC97) and owners of included dogs had given informed consent that their pet's data could be used for clinical research purposes.

References

Acenio, M. J., Brown, S., Coleman, A. E., et al. (2018) AVICM consensus statement: guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. Journal of Veterinary Internal Medicine 32, 1803-1822

Alroy, J., Rush, J. E. & Sarker, S. (2005) Infantile dilated cardiomyopathy in Portuguese water dogs: correlation of the autosomal recessive trait with low plasma taurine levels. Journal of Veterinary Internal Medicine 29, 51-56

Azuma, J., Sawamura, A. & Awata, N. (1992) Usefulness of taurine in chronic congestive heart failure and its prospective application: current therapy of intracorporeal congestive failure, Japanese Circulation Journal 56, 99-99

Backus, R. C., Ko, K. S., Fassett, K. A. J., et al. (2006) Low plasma taurine concentrations in Newfoundland dogs is associated with low plasma methionine and cysteine concentrations and low taurine synthesis. The Journal of Nutrition 136, 2525-2533

Blandanger, M. C., Ouellet, M., Queney, G., et al. (2005) Taurine-deficient dilated cardiomyopathy in a family of golden retrievers. Journal of the American Animal Hospital Association 41, 284-291

Boon, J. A. (1996) The M-Mode and Doppler examination. In: Manual of Veterinary Echocardiography. 2nd edn. Baltimore, MD: Williams & Wilkins. pp 139-205

Boswood, A., Häggestrom, J., Gordon, S. G., et al. (2016) Effect of pimobendan in dogs with preclinical myopathological mitral valve disease and cardiomyopathy: the EPIC study—a randomized clinical trial. Journal of Veterinary Internal Medicine 30, 1765-1779

Chebolt, V. & Tissier, R. (2012) Echocardiographic assessment of canine degenerative mitral valve disease. Journal of Veterinary Cardiology: The Official Journal of the European Society of Veterinary Cardiology 14, 127-148

Cornell, C. C., Kittleson, M. D., Delia Torre, P., et al. (2004) Allometric scaling of M-mode cardiac measurements in normal adult dogs. Journal of Veterinary Internal Medicine 18, 311-321

Delaney, S. J., Kass, P. H., Rogers, Q. R. & Fassett, A. J. (2003) Plasma and whole blood taurine in normal dogs of varying size fed commercially prepared food. Journal of Animal Physiology and Animal Nutrition 87(6), 235-244

Dukes-McEwan, J., Biourge, V., Ridyard, A., et al. (2001) Dilated cardiomyopathy (DCM) in Newfoundland dogs: association with low whole blood taurine level. BSAVA Congress 2001 Scientific Proceedings Abstract 14, p. 500. Journal of Small Animal Practice 42, 365

Dukes-McEwan, J., Borgarelli, M., Tidholm, A., et al. (2003) Proposed guidelines for the diagnosis of canine idiopathic dilated cardiomyopathy. Journal of Veterinary Cardiology 8, 7-19

Dukes-McEwan, J. D. (2000) Canine dilated cardiomyopathy 2. Pathophysiology and treatment. In: Practice 22, 620-628

Dutton, E. & López-Rivera, J. (2018) An update on canine cardiomyopathies—Is it all in the genes? The Journal of Small Animal Practice 59, 455-464

Edgar, S. E., Kirk, C. A., Rogers, Q. R., et al. (1998) Taurine status in cats is not affected by dietary cysteine-sulfinic acid. The Journal of Nutrition 128, 751-757

Fassett, A. J., Reed, J. R., Rogers, Q. R., et al. (2003) Taurine deficiency in dogs with dilated cardiomyopathy: 12 cases (1997-2001). Journal of the American Veterinary Medical Association 223, 1137-1141

Fogle, B. (1996) Cooke Spaniel, American & English. Firefly Books, Willowdale Ford, R. B. & Mazzaferrro, E. (2011) Charts and tables. In: Kirk & Bistner’s Handbook of Veterinary Procedures and Emergency Treatment. 9th edn. Amsterdam: Elsevier Health Sciences. p 646

Fox, P. R., Sisson, D. & Sydney Moïse, N. (1999) Myocardial diseases of dogs. In: Textbook of Canine and Feline Cardiology: Principles and Clinical Practice. 2nd edn. London, UK: WB Saunders Company. pp 681-699

Freeman, L. M., Stern, J. A., Fries, R., et al. (2018) Diet-associated dilated cardiomyopathy in dogs: what do we know? Journal of the American Veterinary Medical Association 253, 909-915

Gavaghan, B. J. & Kittleson, M. D. (1997) Dilated cardiomyopathy in an American Cocker Spaniel with taurine deficiency. Australian Veterinary Journal 75, 862-868

Goodwin, J. P. Robinson, W. F. & Mews, G. C. (1986) Echocardiographic characterisation of dilated cardiomyopathy in the English cocker spaniel. American Journal of Veterinary Research 47, 1978-1983

Gordon, S. G., Edgar, S. E., Kirk, C. A., Rogers, Q. R., et al. (1992) A cardiomyopathy in the English Cocker Spaniel: a clinicopathological investigation. Journal of Small Animal Practice 23, 133-149

Häggestrom, J., Boswood, A., O’Grady, M., et al. (2013) Longitudinal analysis of quality of life, clinical, radiographic, and echocardiographic, and laboratory variables in dogs with myomatosus mitral valve disease receiving pimobendan or benazzi-epil: the QUEST study. Journal of Veterinary Internal Medicine 27, 1441-1451

Hickman, M. A., Bruss, M. L., Morris, J. G., et al. (1997) Results of the multicenter SUST study—a randomized clinical trial. Journal of Veterinary Internal Medicine 11, 204-211

Ko, K. S., Backus, R. C., Berg, J. R., et al. (2007) Differences in taurine synthesis rate among dogs relate to differences in their maintenance energy requirement. The Journal of Nutrition 137, 1171-1175

Kramer, S., Kittleson, M. D., Fox, R. P., et al. (1995) Plasma taurine concentrations in normal dogs and in dogs with heart disease. Journal of Veterinary Internal Medicine 9, 253-258

Luis Fuentes, V., Conoran, B., French, A., et al. (2002) A double-blind, randomized, placebo-controlled study of pimobendan in dogs with dilated cardiomyopathy. Journal of Veterinary Internal Medicine 16, 255-261

Martin, M. W. S., Stafford Johnson, M. J. & Celona, B. (2009) Canine dilated cardiomyopathy: a retrospective study of significance, presentation and clinical findings in 369 cases. The Journal of Small Animal Practice 50, 23-29

Mears, K. M. (2004) Boxer dog cardiomyopathy: an update. Veterinary Clinics: Small Animal Practice 34, 1235-1244

Monnet, E., Orton, E. C., Salman, M., et al. (1995) Idiopathic dilated cardiomyopathy in dogs: survival and prognostic indicators. Journal of Veterinary Internal Medicine 9, 12-17

Oortwijn, E. S., Welsh, B. D., Yu, J., et al. (2020) Development of plasma and whole blood taurine reference ranges and identification of dietary features associated with taurine deficiency and dilated cardiomyopathy in golden retrievers: a prospective, observational study. PLoS One 15, 5

Pedro, B. M., Alves, J. V., Cripps, P. J., et al. (2011) Association of QRS duration and survival in dogs with dilated cardiomyopathy: a retrospective study of 266 clinical cases. Journal of Veterinary Cardiology 13, 243-249

Pion, P. D., Kittleson, M. D., Rogers, Q. R., et al. (1987) Myocardial failure in cats associated with low plasma taurine: a reversible cardiomyopathy. Science 237, 764-768

Sahn, D. J., DeMaria, A., Kjoss, J., et al. (1978) Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 58, 1072-1083

Sanderson, S. L. (2008) Taurine and carnitine in canine cardiomyopathy. Veterinary Clinics: Small Animal Practice 36, 1325-1343

Sanderson, S. L., Osborne, C. A., Lulich, J. P., et al. (2001) Evaluation of urinary carnitine and taurine excretion in 5 cystinuric dogs with carnitine and taurine deficiency. Veterinary Journal of Internal Medicine 15, 94-100

Schober, K. E., Hart, T. M., Stern, J. A., et al. (2010) Detection of congestive heart failure in dogs by Doppler echocardiography. Journal of Veterinary Internal Medicine 24, 1398-1404

Shimbrin, J. S., Wood, M. A., Jensen, D. N., et al. (1997) Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. Journal of the Elephantine College of Cardiology 29, 709-715

Spence, S., French, A., Penderik, M., et al. (2019) The occurrence of cardiac abnormalities in canine steroid-responsive meningitis arteritis. Journal of Small Animal Practice 60, 204-211

Summerfield, N. J., Boswood, A., O’Grady, M. R., et al. (2012) Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in Doberman-
Pinschers with preclinical dilated cardiomyopathy (the PROTECT study). *Journal of Veterinary Internal Medicine* **26**, 1337-1349
Thomas, R. E. (1987) Congestive cardiac failure in young Cocker Spaniels (a form of cardiomyopathy?): details of eight cases. *Journal of Small Animal Practice* **28**, 265-279
Thomas, W. P., Gaber, C. E., Jacobs, G. J., et al. (1994) Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat. *Veterinary Radiology and Ultrasound: The Official Journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association* **35**, 173-178
Tidholm, A., Svensson, H. & Sylvén, C. (1997) Survival and prognostic factors in 189 dogs with dilated cardiomyopathy. *Journal of the American Animal Hospital Association* **33**, 364-368
Tôrres, C. L., Backus, R. C. Fascetti, A. J. & Rogers, Q. R. (2003) Taurine status in normal dogs fed a commercial diet associated with taurine deficiency and dilated cardiomyopathy. *Journal of Animal Physiology and Animal Nutrition* **87**, 359-372
Van Vleet, J. F. & Ferrans, V. J. (1986) Myocardial diseases of animals. *The American Journal of Pathology* **124**, 98
Vollmar, A. C., Fox, P R., Servet, E., et al. (2013) Determination of the prevalence of whole blood taurine in Irish wolfhound dogs with and without echocardiographic evidence of dilated cardiomyopathy. *Journal of Veterinary Cardiology: The Official Journal of the European Society of Veterinary Cardiology* **15**, 189-196
Wotton, P R. (1998) Cardiomyopathy in English cocker and springer spaniels: a review of 38 cases. *Proceedings of the British Small Animal Veterinary Association*, p316