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Original Article

Cats with diabetes mellitus have diastolic dysfunction in the absence of structural heart disease

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Abstract

Diabetes mellitus (DM) can result in cardiovascular dysfunction and heart failure characterized by diastolic dysfunction with or without the presence of systolic dysfunction in people and laboratory animals. The objective of this prospective study was to determine if cats with newly diagnosed DM had myocardial dysfunction and, if present, whether it would progress if appropriate antidiabetic therapy was commenced. Thirty-two diabetic cats were enrolled and received baseline echocardiographic examination; of these, 15 cats were re-examined after 6 months. Ten healthy age- and weight-matched cats served as controls.

Diabetic cats at diagnosis showed decreased diastolic, but not systolic function, when compared to healthy controls, with lower mitral inflow E wave (E) and E/E' than controls. After 6 months, E and E/IVRT' decreased further in diabetic cats compared to the baseline evaluation. After excluding cats whose DM was in remission at 6 months, insulin-dependent diabetic cats had lower E, E/A and E' than controls. When classifying diastolic function according to E/A and E'/A', there was shift towards impaired relaxation patterns at 6 months. All insulin-dependent diabetic cats at 6 months had abnormal diastolic function. These results indicate that DM has similar effects on diastolic function in feline and human diabetics. The dysfunction seemed to progress rather than to normalize after 6 months, despite antidiabetic therapy. In cats with pre-existing heart disease, the development of DM could represent an important additional health risk.

Keywords: Cats; Diabetes mellitus; Diastolic function; Echocardiography; Tissue Doppler imaging

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Introduction

In humans, the concept of diabetic angiopathy was originally suggested in 1954 (Lundbaek, 1954) and diabetic cardiomyopathy was first described in 1972 (Rubler et al., 1972). More recently, researchers have demonstrated that diabetes mellitus (DM) is an independent risk factor for the development of heart failure (Kannel et al., 1974; Aronow and Ahn, 1999; Gottdiener et al., 2000). Patients with DM and concomitant cardiovascular disease have a poorer prognosis compared to those with only cardiovascular disease (Stone et al., 1989). Additionally, type 2 human diabetics commonly have left ventricular diastolic dysfunction without clinically detectable heart disease (Poirier et al., 2001). Recently, diabetic cardiomyopathy has been defined as the existence of left ventricular dysfunction in diabetic patients without coronary artery disease, hypertension or other potential causes (Ernande and Derumeaux, 2012).

Few studies have examined the existence of cardiovascular consequences of DM in veterinary medicine. One study found congestive heart failure (CHF) to be the most commonly associated condition in cats with hyperglycemia (Laluha et al., 2004). In that study, CHF was considered the primary condition and stress hyperglycemia was concurrent. However, that study could not determine if in individual cases hyperglycemia was due to recently developed DM and was potentially the cause of acute CHF in previously unrecognized stable heart disease (Laluha et al., 2004). Heart disease and CHF was common in diabetic cats in another study (Little and Gettingby, 2008), but those cats had a range of cardiac disorders and causal relationships were not established. Importantly, cardiac function has never been specifically studied in cats with DM.

We sought to assess cardiac function in feline patients with newly diagnosed DM and to characterize the further development over the course of 6 months. We hypothesized that cats with DM would show evidence of cardiac dysfunction at the time of diagnosis, which would normalize over time with successful antidiabetic therapy.

Materials and methods

Inclusion and exclusion criteria, diabetic cats and control cats

Cats presenting to the Clinic for Small Animal Internal Medicine of the University of Zurich with spontaneously occurring DM, newly diagnosed or diagnosed within the previous 4 weeks, were prospectively enrolled in the study. Cats were excluded if they had structural heart disease, or concomitant systemic disease that might affect cardiac function, such as hypersomatotropism, hyperthyroidism, systemic hypertension (defined as systolic blood pressure >160 mmHg; Brown et al., 2007), severe anemia (defined as haematocrit <18%; Wilson et al., 2010), recent glucocorticoid treatment (Smith et al., 2004), or severe underlying disease that was expected to complicate diabetic control or markedly shorten life expectancy. Blood pressure was measured using either the indirect Doppler technique (Ultrasound Doppler Flow Detector, Parks Medical Electronics) or an oscillometric device (HDO Vet Blood Pressure Monitor, DVM Solutions) after a short adaptation period in a quiet environment (Brown et al., 2007). The lowest and highest of at least five consecutive measurements were excluded and an average value was then calculated.

All cats underwent physical examination, complete blood count, biochemical profile, urinalysis (including protein-creatinine ratio and bacterial culture), serum fructosamine, beta-

hydroxybutyrate, feline pancreatic lipase immunoreactivity, thyroxine (T4) and insulin-like growth factor 1, thoracic and abdominal radiographs and abdominal ultrasound. Additionally, cats underwent CT when deemed necessary to corroborate hypersomatotropism. The standard antidiabetic therapy included insulin glargine twice daily, and a low carbohydrate, high protein diet (Purina DM, Société des Produits Nestle). Additionally, six cats received an extended-release glucagon-like peptide-1 (GLP-1) analogue, exenatide, as part of another study (Riederer et al., 2014). Diabetic remission during the course of the study was defined as being clinically unremarkable, and maintaining normal blood glucose and fructosamine concentrations without insulin therapy for at least 1 month after cessation of treatment (Sieber-Ruckstuhl et al., 2008; Zini et al., 2010). Echocardiographers were masked to each cat's diabetic control status at the 6-month examination. Ten healthy age- and weight-matched cats, imaged during the same period, served as controls. The study was approved by the State Veterinary Office of Zurich (Application numbers 122/2011, approved July 7, 2011, and 118/2014, approved June 17, 2014).

Echocardiography

Recruited cats underwent echocardiography, unsedated, by a board-certified cardiologist or a cardiology resident at the time of diagnosis (DM_0), followed by a re-evaluation at 6 months post-diagnosis (DM_6) after they had been rehydrated (if considered dehydrated at presentation). Dehydration was estimated at admission and corrected over the first 12 h; when rehydrated, fluid rate was decreased to maintenance rate (3 mL/kg/h). Examinations were performed with a Vivid 7 (GE Medical Systems) using a 7S or a 10S probe, with simultaneous ECG acquisition. Echocardiographic planes were acquired according to published guidelines (Thomas et al., 1993). Quantitative 2-dimensional (2D) data from right parasternal views included long axis left

atrial diameter (LAD), and short axis left atrial to aortic diameter ratio (LA/Ao), M-Mode short axis interventricular septum thickness in diastole (IVSd), left ventricular internal diameter in diastole (LVIDd), left ventricular free wall in diastole (LVFWd) and left ventricular fractional shortening (FS). Absence of structural heart disease was defined as qualitatively normal appearance of all four chambers on 2D echocardiography, and quantitatively normal left atrial size (2D LA/Ao in short axis < 1.5) and normal LV wall thickness in diastole (2D or M-Mode ≤5.5 mm; Christiansen et al., 2015).

Quantitative pulsed wave (PW) Doppler and tissue Doppler imaging (TDI) variables were recorded from the left apical four chamber view and included mitral inflow E (E) and A (A) waves, E/A ratio (E/A), TDI isovolumic relaxation time (IVRT'), E to IVRT' ratio (E/IVRT'), TDI systolic wave (S'), TDI early (E') and atrial diastolic wave (A'), E'/A' ratio (E'/A'), and E to E' ratio (E/E'). For E and A wave velocities, a PW sample volume of 2 mm was placed between the tips of the opened mitral valve leaflets as previously described (Schober and Chetboul, 2015). The E/A was not calculated when the E and A were completely or partially fused (E-at-A velocity > 20 cm/s; Schober et al., 2003). The TDI variables were recorded at the level of the mitral valve annulus of the left ventricular free wall. IVRT' was defined as the period between the end of the S' to the beginning of the E' with a PW sample volume of 1 mm (Koffas et al., 2006); E/A, E/E' and E/IVRT' were subsequently calculated. Sweep speed during analysis was 200 mm/s.

Diastolic function was classified according to mitral Doppler inflow and TDI measurements into normal (E/A 1-2 and E'/A' >1), delayed relaxation (E/A <1 and E'/A' <1),

pseudonormal (E/A 1-2, E'/A' <1) or restrictive (E/A >2 and E'/A' <1) patterns (Schober and Chetboul, 2015). Systolic function was assessed using FS and S´.

Statistical analysis

Data were analysed for normality using the Shapiro-Wilk test at an α level of 0.05. Mean and standard deviation for individual echocardiographic variables were then calculated. A two sample *t*-test was performed to compare diabetic cats at the time of diagnosis and control cats. A paired sample *t*-test was used to compare diabetic cats at the time of diagnosis and at 6 months post-diagnosis. Calculations were performed initially by including cats in diabetic remission at 6 months, and then by excluding these cats at both time points (DM_{0nr}, diabetics at time of diagnosis excluding those with DM in remission at 6 months; DM_{6nr}, diabetics at 6 months post-diagnosis excluding those with DM in remission; $DM0_r$, diabetics at the time of diagnosis that progressed to diabetic remission; DM_{6r}, diabetics in remission at 6 months post-diagnosis). Comparison of diastolic function patterns between and within groups was performed using Chi-square and McNemar analysis, respectively. The effect of age on parameters of diastolic function was calculated using the Pearson correlation test. Cats with fused E waves were excluded from all analyses. Statistical significance was set at $P < 0.05$ for all comparisons. Data are presented as mean ± standard deviation [range]. Graphs and statistical analyses were performed using commercially available software (SPSS Statistics, IBM).

Results

Between May 2013 and October 2014, 50 cats were screened for inclusion. Eighteen cats were subsequently excluded for the following reasons: evidence of structural heart disease (*n*=4;

two of these cats developed dyspnea at presentation to the hospital and showed radiographic evidence of CHF and echocardiographic evidence of left ventricular hypertrophy); DM due to hypersomatotropism (*n*=3); DM of >4 weeks duration (*n*=2); clinical signs and findings consistent with severe pancreatitis (*n*=2); evidence of neoplastic disease (*n*=2); severe anemia (*n*=1); hyperthyroidism (*n*=1); hypertension (*n*=1); cholecystitis (*n*=1); and asthma (*n*=1).

The remaining 32 cats were included in the study. The study population included Maine Coon (*n*=2), Norwegian Forest (*n*=2) and Domestic short haired (DSH) cats (*n*=28); 18 were female and 14 were male. Cats were 10.8 ± 3.4 [4-19] years old and weighed 4.97 ± 1.27 [3.0-7.7] kg. All cats were treated with glargine and six cats were also treated with GLP-1. The ten control cats were DSH (*n*=4), Maine Coon (*n*=2), Domestic longhair (*n*=1), Bengal (*n*=1), Burmese (*n*=1) and Persian (*n*=1), aged 9.2 ± 4.3 [3-17] years and weighing 4.17 ± 1.07 [3-6.3] kg. Diabetic and control cats did not differ in age (*P*=0.216), bodyweight (*P*=0.08) or blood pressure measurements (*P*=0.89).

Fifteen of the 32 diabetic cats included in the study presented to the 6 month recheck examination. Of the 17 cats that failed to present at 6 months, five died (undiagnosed causes, *n*=4; diabetic ketoacidosis, *n*=1); three owners declined follow up appointments; and the remaining nine were lost to follow up. Of the 15 cats remaining in the study, five were in diabetic remission at 6 months. Of the six cats receiving GLP-1 at inclusion, five were followed up at 6 months (three underwent remission). Fructosamine concentrations were as follows: DM_0 – 623 ± 98 [418 - 775] µmol/L; DM_6 – 377 ± 122 [256 - 616] µmol/L; DM_{6nr} – 405 ± 112 [258 - 616] µmol/L; DM_{6r} – 279 ± 28 [256 - 330] µmol/L (reference interval: 200 – 340 µmol/L).

No differences were observed in 2-D and M-Mode parameters between the groups at baseline (Table 1). No cat exhibited abnormalities in systolic function, quantified by M-Mode FS and pulsed-wave Doppler tissue imaging (PWDTI) S', at any time. Age did not correlate with any echocardiographic variables. Assessment of both E/A and E'/A' was possible for five control cats, 23 diabetic cats at diagnosis, 12 cats at 6 months and seven cats at 6 months, after excluding cats in remission. In the other cats, these variables could not be measured, because of fused E and A waves. At diagnosis, diabetic cats had lower E (P=0.008) and E/E´ (P=0.04) than control cats (Table 1). At 6 months, diabetic cats had lower E (P=0.005), E/IVRT' (P=0.12) and heart rate (P=0.11) than at baseline (Table 1). Diabetic cats that failed to undergo remission at 6 months (DM_{6nr}) had lower E velocities (P=0.022), E/A (P=0.029), and E' velocities (P=0.018) than control cats and lower E' (P=0.003), E'/A' (P=0.23) and higher E/E' (P=0.034) than diabetic cats that underwent remission ($DM6_r$; Table 1).

Abnormal diastolic function patterns were more prevalent in diabetic cats at 6 months (DM_6; P=0.013) and diabetic cats not in remission ($DM6_{nr}$; P=0.006) than in control cats (Table 2). Of the cats that did not undergo diabetic remission, one that initially had a normal diastolic function pattern progressed to a delayed relaxation pattern at 6 months, and three other cats that initially had delayed relaxation progressed to a pseudonormal pattern. Of the cats that underwent diabetic remission (DM_{6r}), one that initially had normal function remained normal; two that initially had normal function developed delayed relaxation patterns; and one that initially had a pseudonormal pattern reverted to a delayed relaxation pattern (Fig. 1). None of the cats showed a restrictive pattern of diastolic function (Table 2).

Discussion

This is the first study to specifically evaluate cardiac function in diabetic cats, and our results suggest that DM affects diastolic cardiac function. This dysfunction is apparent in cats prior to instituting antidiabetic therapy, and persists or progresses in cats that fail to undergo remission after 6 months of therapy, but possibly improves in cats that undergo remission.

In humans, diabetic cardiomyopathy is defined as the presence of cardiac dysfunction in diabetic patients, when other causes of heart disease such as coronary artery disease or systemic hypertension have been excluded (Ernande and Derumeaux, 2008). Several predisposing factors have been suggested for human diabetic cardiomyopathy, e.g., severe coronary atherosclerosis and prolonged hypertension. However, the recent definition of diabetic cardiomyopathy excludes these factors (Ernande and Derumeaux, 2008). The following pathogenic factors are currently implicated: chronic hyperglycaemia, microvascular disease (Shapiro et al., 1981), glycosylation of myocardial proteins, autonomic neuropathy (Grundy et al., 1999; Fang et al., 2004; Maisch et al., 2011; Amaral and Okonko, 2015) and altered cellular calcium handling (Allo et al., 1991; Pierce and Russel, 1997; Belke and Dillmann, 2004). Additionally, increased concentrations of free fatty acids, leading to accelerated fat metabolism and development of reactive oxygen species, have been suggested as pathogenic factors (Boudina and Abel, 2007). Experimentally, uncontrolled DM produces progressive myocardial damage consisting of loss of myofibrils and mitochondria, deposition of extracellular matrix and decrease of capillary density, that can only partially be reversed by insulin treatment (Thompson et al., 1994). At a molecular level, defects in calcium movement by various transporters with abnormal cytosolic calcium regulation, and a

232 reduction in sarcoendoplasmic reticulum calcium ATPase activity have also been reported (Allo
233 et al., 1991). Abnormal calcium handling is not only responsible for abnormal contractile and
234 diastolic function, but increased intracellular free calcium could also be responsible for
235 cardiomyocyte damage (Pierce and Russel., 1997; Belke and Dillmann, 2004).
236
237 Distinct phenotypes in diabetic cardiomyopathy have been proposed (dilated phenotype
238 with reduced ejection fraction and restrictive phenotype with preserved ejection fraction), but it
239 is not completely clear whether they represent different pathophysiological mechanisms or
240 simply different stages of the same disease process, with early diastolic dysfunction preceding
241 systolic dysfunction (Schannwell et al., 2002; Teupe and Rosak, 2012; Pham et al., 2015;
242 Seferovic and Paulus, 2015). Experimentally, systolic and diastolic dysfunction characterized by
243 reduced FS and reduced E/A were found in 12-week old transgenic diabetic mice. These results
244 were considered evidence of diabetic cardiomyopathy caused by altered cardiac metabolism
245 (Semeniuk et al., 2002).
246
247 In small animals, few studies have looked at the association between DM and
248 cardiovascular disease and their potential effects on cardiac function. Heart murmurs or gallop
249 rhythms have been observed in approximately 25% of diabetic cats, but specific cardiac
250 abnormalities were not reported (Crenshaw and Peterson, 1996; Nelson et al., 2000). However,
251 heart murmurs are also common in healthy cats and heart disease can be present in cats without
252 audible heart murmurs (Côté et al., 2004; Paige et al., 2009; Nakamura et al., 2011).
253 Additionally, previous studies have reported the development of CHF in diabetic feline patients
254 (Rush et al., 2002; Koenig et al., 2004). A more recent retrospective study reported that CHF was

common among diabetic cats. Diabetic cats had a 10-fold increased risk of CHF compared to age-matched control cats, and of 14 diabetic cats, CHF was the reason for euthanasia in six. However, primary heart disease was probably present in these cats, specifically hypertrophic cardiomyopathy in three, and it is not known if CHF was a diabetic complication or vice versa (Little and Gettingby, 2008).

In our study, cats with evidence of concomitant structural heart disease, such as HCM, were excluded, to rule-out visible underlying heart disease as cause of dysfunction. We did not identify evidence of systolic dysfunction in any cats. However, we frequently observed left ventricular diastolic dysfunction at the time of diagnosis. Furthermore, diastolic dysfunction seemed to progress rather than normalize over time, despite antidiabetic therapy, in cats that did not undergo remission. The simultaneous decrease in E and E/E' could be explained by relaxation abnormalities or decreases in left ventricular filling pressures, potentially due to polyuria/polydipsia and/or variable states of dehydration, hypovolemia or shock in diabetic cats at presentation. Volume depleted cats would also be expected to have decreased end diastolic pressures and therefore increased left ventricular and atrial compliance, leading to a decrease in E wave measurements (Schober et al., 2003). Hypovolemia should not have been an important cause of measurement error in this study because in order to avoid dehydration as confounding factor, we only performed echocardiography when cats were considered rehydrated. However, even at 6 months, we cannot exclude the possibility that DM_{6nr} had a different hydration status than DM_{6r}.

Our findings agree with reports in humans. In one study, left ventricular diastolic dysfunction was considered common in type 2 diabetic patients who had been stable for a minimum of 3 months, without any clinically detectable heart disease. Diastolic dysfunction affected 60% of these patients; 28% showed a pseudonormal pattern and 32% a delayed relaxation pattern (Poirier et al., 2001). Similarly, we identified diastolic dysfunction in 82% (n=10) of DM_6 cats; there was a delayed relaxation in seven cats and a pseudonormal pattern in three cats. Further, all cats in the DM_{6nr} group showed either persistent or progressive diastolic dysfunction; five had delayed relaxation and two had pseudonormalization. In another study, recently diagnosed human type 2 diabetics had preclinical E and E/A abnormalities (Robillon et al., 1994). We also identified lower E velocities in the DM_6 group, as well as lower E/A and E´ in the DM_{6nr} group.

In diabetic humans, a relationship between glycemic control and risk of developing heart failure has been established (Iribarren et al., 2001); even acromegalic patients undergoing surgical therapy and subsequent improvement in glycemic control improve their diastolic functional class (Minniti et al., 2001). Accordingly, optimal glycemic control is considered an important tool to prevent or mitigate the development of diabetic cardiomyopathy (Grundy et al., 1999). Similarly, glycemic control appears to have influenced our results. In our study, 33% of diabetic cats underwent remission, while in persistently diabetic cats, insulin treatment had the intended metabolic effects, as evidenced by normalization of clinical signs, lowering of serum glucose and decrease in fructosamine concentrations over the 6 months observation period. However, the DM_{6nr} group had more abnormal diastolic function than the DM_{6r} group, including higher E´, E´/A´ and reduced E/E´, suggesting improvement of diastolic function and lower LV

300 filling pressures in the absence of DM. Importantly, correction of metabolic derangements with
301 insulin in the DM_{6nr} group did not necessarily improve diastolic function, as evidenced by
302 persistent dysfunction compared with baseline measurements and with control cats.
303
304 The non-normalized fructosamine concentrations in some of the DM_{6nr} group at 6 months
305 imply that diabetic control was not perfect, which might explain why diastolic dysfunction
306 progressed despite therapy. Without an untreated diabetic control group, we cannot know if cats
307 not receiving therapy would have progressed more rapidly or severely into a more advanced
308 stage of diastolic dysfunction, or even have developed systolic dysfunction, and eventually CHF.
309 However, it would be unethical not to treat diabetic cats with insulin.
310
311 This study had several limitations. The number of cats enrolled and in particular, the
312 number of cats followed up at 6 months, was small, and the timespan of our observation period
313 was relatively short. Therefore, it is possible that more subtle changes in diastolic variables,
314 especially in the DM_{6r} group, might have gone undetected. Pulmonary vein flow and color M-
315 mode flow propagation velocities were not measured, and could have provided additional
316 information to help classify diastolic function (Schober et al., 2003). Essentially, every cat had
317 been receiving fluids as supportive therapy. Hydration status clearly affects morphological
318 dimensions and systolic and diastolic echocardiographic parameters of cardiac function (Schober
319 et al, 2003; Campbell and Kittleson, 2007). Even though at the time of echocardiography all cats
320 were considered euvolemic, and fluids were given at maintenance rates at the time of initial
321 echocardiography, the assessment of hydration status is subjective and not exact. Interestingly,
322 the borderline high LA diameter in one cat suggest mild volume overload. Some cats were

concurrently enrolled in a study assessing the effect of a GLP-1 analogue on glycemic control. The cardiovascular effects of GLP-1 agonists are not well studied in cats. In dogs with pacing-induced dilated cardiomyopathy, recombinant GLP-1 led to a significant increase in LV ejection fraction, cardiac output and lowering of systemic vascular resistance (Nikolaidis et al., 2004). GLP-1 seems to be cardio protective, potentially augmenting myocardial contractility under conditions of metabolic stress, with stimulation of myocardial glucose uptake as one major underlying mechanism (Grieve et al., 2009). GLP-1 and analogues have also been demonstrated to have a direct vasorelaxant action (Treiman et al., 2010). We cannot exclude the possibility that the GLP-1 analogue led to masking of underlying systolic dysfunction or altered diastolic function. Finally, we do not know the duration of diabetes in enrolled cats at the time of diagnosis. Obviously, in order for DM to affect cardiac function, a certain time span of uncontrolled glucose metabolism is necessary. Extrapolations from an experimental study in mice suggest a few weeks is sufficient (Semeniuk et al., 2002). Diabetes can have an insidious onset, and it seems likely that in our cats DM was present for at least a few weeks.

Conclusions

Our results suggest that diastolic dysfunction is common in diabetic cats at the time of diagnosis, and over the following 6 months an increase in the prevalence of diastolic dysfunction can occur, despite antidiabetic therapy. These observations indicate that diabetic cardiomyopathy might be an entity in cats, similar to in humans. Whether the dysfunction identified here becomes clinically apparent, or exacerbates pre-existing, coincidental cardiac disease, is unknown.

Conflict of interest statement

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