Systolic blood pressure in cats with diabetes mellitus

Kathleen A. Sennello, DVM; Rhonda L. Schulman, DVM, DACVIM; Robert Prosek, DVM; Arthur M. Siegel, DVM, PhD

Objective—To determine the prevalence of systemic hypertension in cats with diabetes mellitus and establish ranges for echocardiographic variables in diabetic cats.

Design—Prospective study.

Animals—14 cats with diabetes mellitus and 19 healthy control cats.

Procedure—Systolic blood pressure was measured indirectly with a noninvasive Doppler technique. Ophthalmic and echocardiographic examinations were performed, and urine protein concentration was measured. Cats were considered to have hypertension if they had systolic blood pressure > 180 mm Hg and at least 1 other clinical abnormality typically associated with hypertension (eg, hypertensive retinopathy, left ventricular hypertrophy, or proteinuria).

Results—None of the diabetic or control cats had systolic blood pressure > 180 mm Hg. One diabetic cat had left ventricular hypertrophy, but systolic blood pressure was 174 mm Hg. None of the cats had evidence of hypertensive retinopathy or proteinuria. Mean values for echocardiographic variables for the diabetic cats were not significantly different from published values for healthy cats.

Conclusions and Clinical Relevance—Results suggest that hypertension does not occur or occurs in only a small percentage of cats with diabetes mellitus. (J Am Vet Med Assoc 2003;223:198–201)

Hypertension is common in humans with diabetes mellitus and contributes greatly to the development of diabetic nephropathy, neuropathy, cardiomyopathy, and retinopathy. The prevalence of hypertension in diabetic human patients reportedly ranges from 40 to 80%, with prevalence and severity increasing as glycemic control decreases and duration of disease increases. In fact, hypertension is so common in humans with diabetic nephropathy and develops so early in the course of the disease that strict control of blood pressure, as opposed to control of blood glucose concentration, results in improvement of renal function and slows progression of the nephropathy. In these patients, demonstrable microalbuminuria is the hallmark of subclinical, possibly progressive renal disease.

Recent evidence suggests that the prevalence of hypertension in dogs with diabetes mellitus (46%) is similar to the prevalence in humans, with prevalence increasing as the duration of disease increases. To our knowledge, however, the prevalence of hypertension in cats with diabetes mellitus has not been reported. On the other hand, diabetes mellitus has been linked to chronic pancreatitis, retinopathy, obesity, and neuropathy in cats. In addition, hypertension is being diagnosed with increasing frequency in older cats, in part because of increases in life span but primarily because of increased recognition of the condition. Common clinical signs of hypertension in cats included ocular abnormalities associated with hypertensive retinopathy and heart murmurs associated with left ventricular hypertrophy. Hypertension is most commonly secondary to chronic renal failure and hyperthyroidism, with primary hypertension being relatively rare. The purposes of the study reported here were to determine the prevalence of systemic hypertension in cats with diabetes mellitus and establish ranges for echocardiographic variables in diabetic cats.

Materials and Methods

Cats—Fourteen cats with diabetes mellitus examined at the University of Illinois Veterinary Teaching Hospital and 19 healthy control cats were included in the study. In the cats with diabetes mellitus, the diagnosis was made on the basis of appropriate clinical signs (eg, polyuria and polydipsia), high serum glucose concentration (> 250 mg/dL), and detection of glucose in the urine with a dipstick. To rule out stress glycosuria as the cause of the high serum glucose concentration, cats were included in the study only if serum fructosamine concentration had been found to be high (> 285 μmol/L) during the preceding 12 months or if a 24-hour blood glucose concentration curve demonstrated persistent hyperglycemia. To exclude cats with confounding diseases, cats were included only if serum thyroxine (T4) concentration, measured within the preceding 12 months, was within reference limits and a urinalysis performed during the same period did not reveal protein or if results of bacterial culture of a urine sample were negative. Cats with diabetic ketoacidosis that had ketones in their urine were excluded from the study, as were cats with evidence of severe concurrent disease. None of the diabetic or control cats were receiving any medications known to have effects on blood pressure.

Age distribution of the control cats was similar to that of the diabetic cats. Control cats were considered healthy on the basis of results of a physical examination, CBC, serum biochemistry panel (including measurement of serum T4 concentration), and urinalysis.

Because hypertension is more common in human patients with poorly controlled diabetes, the degree of glycemic control in diabetic cats was evaluated by measuring serum fructosamine concentration9 and calculating mean blood glucose (MBG) concentration during a 24-hour period. Fructosamine concentrations < 350 μmol/L were considered evidence of excellent glycemic control, between 350 and 450 μmol/L were considered evidence of good control,
between 450 and 600 µmol/L were considered evidence of fair control, and > 600 µmol/L were considered evidence of poor control. An MBG concentration < 200 mg/dL was considered evidence of excellent glycemic control, between 200 and 300 mg/dL was considered evidence of good control, between 300 and 400 mg/dL was considered evidence of fair control, and > 400 mg/dL was considered evidence of poor control. In cats in which fructosamine and MBG concentrations were both determined, both values were used to classify glycemic control. As a result, some cats were assigned to 2 categories.

**Measurement of systolic blood pressure**—Systolic blood pressure was measured indirectly with a Doppler flow detector incorporating a 9.6 MHz probe and neonatal No. 2 inflatable cuff with a width approximately 30% of the limb circumference. Cats were gently restrained without sedation in lateral recumbency for blood pressure measurement, and the blood pressure cuff was placed just proximal to the tarsal joint. A transducer with coupling gel was positioned and adjusted distal to the cuff on the medial aspect of the limb until a clear signal could be detected from the cranial tibial artery. The cuff was then inflated to approximately 20 mm Hg greater than the pressure when an audible signal could no longer be detected. A manometer was used to measure the pressure. Multiple measurements of systolic blood pressure were obtained during a 5- to 10-minute period, and the most consistent 5 values were averaged to determine systolic blood pressure for each cat. For purposes of this study, cats were considered to have high systolic blood pressure if pressure was > 180 mm Hg.

Because the stress of examination and hospitalization may cause transient increases in systolic blood pressure, cats were considered to have systemic hypertension only if systolic blood pressure (mean of 5 blood pressure measurements obtained over a 5- to 10-minute period) was > 180 mm Hg and if characteristic ophthalmic or echocardiographic changes were seen.

**Ophthalmic evaluation**—In each cat, the fundus was examined by means of indirect ophthalmoscopy for evidence of hypertension. Ophthalmic tropicamide solution was used to dilate the pupils. Cats were specifically examined for signs of retinal detachment, vitreal or retinal hemorrhage, hypHEMA, and vascular tortuosity.

**Urinalysis**—Urine samples were obtained by means of cystocentesis. Urine protein concentration was determined with a validated automated benzethonium chloride turbidity assay. Urine creatinine concentration was determined with a spectrophotometer. Urine protein-to-creatinine ratios > 1 were considered abnormal.

**Cardiac evaluation**—Echocardiography was performed with a 5- or 10-MHz probe. Routine M-mode measurements were obtained with cats in right lateral recumbency, in accordance with published guidelines. The following values were measured: diameter of the left atrium, diameter of the aorta, systolic left ventricular diameter, diastolic left ventricular diameter, systolic left ventricular posterior wall thickness, diastolic left ventricular posterior wall thickness, systolic interventricular septum thickness, and diastolic interventricular septum thickness. Each value was measured for 5 consecutive beats, and the mean value was used for statistical analyses. Pathologic hypertrophy was diagnosed if diastolic interventricular septum thickness or diastolic left ventricular posterior wall thickness was > 6 mm. Left atrial enlargement was diagnosed if the diameter of the left atrium was > 13 mm.

**Statistical analyses**—A Student t test was used to compare systolic blood pressure between diabetic and control cats. Pearson correlation coefficients were calculated to determine whether age was significantly correlated with blood pressure for cats in each group and all cats in the study. For all statistical analyses, a value of P < 0.05 was considered significant.

**Results**

**Cats**—The 14 diabetic cats consisted of 10 males and 4 females. Twelve were domestic shorthairs, 1 was a Maine Coon, and 1 was a Tonkinese. The 19 control cats consisted of 11 males and 8 females. Sixteen were domestic shorthairs, 1 was a Himalayan, and 2 were Siamese. Diabetic cats ranged from 2 to 16 years old (mean, 11.6 years; median, 12 years); control cats ranged from 4 to 17 years old (mean, 11.4 years; median, 12 years).

All of the diabetic cats received insulin as part of their treatment. Three of the 14 diabetic cats had transient diabetes, with periods when they did not require insulin treatment prior to inclusion in the study. However, at the time of inclusion in the study, all 3 cats required insulin treatment to control hyperglycemia. For the remaining 11 diabetic cats, median duration of diabetes mellitus was 18 months (range, 1 week to 62 months).

Serum fructosamine concentration had been measured during the preceding 12 months in 10 of the 14 diabetic cats. Mean concentration was 509 µmol/L (range, 368 to 804 µmol/L). Mean blood glucose concentration had been measured in 9 diabetic cats. Mean concentration was 334 mg/dL (range, 254 to 472 mg/dL). Overall, 3 cats were classified as having poor glycemic control, 1 was classified as having fair-to-poor control, 6 were classified as having fair control, 1 was classified as having fair-to-good control, and 3 were classified as having good control.

**Systolic blood pressure**—None of the diabetic or control cats were considered to have systemic hypertension. Mean ± SD systolic blood pressure for the control cats was 157 ± 9.8 mm Hg (median, 161 mm Hg).

For the diabetic cats, mean systolic blood pressure was 161 ± 17 mm Hg (median, 167 mm Hg). Ocular examinations were performed in all 14 cats, and none had any ocular abnormalities. Urine protein concentration was measured in 12 cats, and none had proteinuria. Echocardiography was performed on 13 cats, and 1 had left ventricular hypertrophy. However, systolic blood pressure in this cat was 174 mm Hg; therefore, the cat was not considered to have systemic hypertension.

Mean systolic blood pressure was not significantly different between diabetic and control cats. Age was not significantly correlated with systolic blood pressure (P = 0.09).

**Echocardiographic findings**—Echocardiography was performed on 13 of the diabetic cats. One had evidence of left ventricular hypertrophy, and 4 had evidence of left atrial enlargement. Compared with published echocardiographic values for healthy cats, diabetic cats had left ventricular free wall and interventricular septum measurements within reference ranges. Mean values for echocardiographic variables for the diabetic cats were not significantly different from published values for 79 healthy cats (Table 1).
Discussion

The organs and tissues most susceptible to the long-term effects of hyperglycemia include the kidney, retina, and nervous tissue, all of which do not depend on insulin for glucose uptake. These are the same organs and tissues most likely to be damaged by sustained hypertension. The prevalence of hypertension in diabetic cats in the present study was 0%, with a 95% confidence interval of 0 to 19%. This is in contrast to findings in humans and dogs in which diabetes, hypercholesterolemia, and hypertension are common. It is also surprising considering that hypertension has been identified in 61% to 65% of cats with renal insufficiency and in 23% to 87% of cats with hyperthyroidism. Efforts were made in the present study to screen out cats with other conditions known to be associated with hypertension, leaving only those individuals having primary hypertension or hypertension related to diabetes mellitus.

The mechanisms behind the development of hypertension in diabetic humans are complex and not fully understood. In patients with type I diabetes, nephropathy is often the basis for hypertension, with contributing factors including extracellular fluid volume expansion, insulin resistance or hyperinsulinemia, activation of the renin-angiotensin-aldosterone system, altered sensitivity to vasopressors, and impaired production of vasodilator and natriuretic factors. In humans, this form of diabetes is typically characterized as juvenile onset with insulin dependence but, more importantly, is defined by insulin resistance or hyperinsulinemia, activation of the renin-angiotensin-aldosterone system, altered sensitivity to vasopressors, and impaired production of vasodilator and natriuretic factors. In humans, it takes, on average, 15 to 20 years of active diabetes for retinal lesions to develop and 12 to 20 years for nephropathy to develop. With better understanding of the disease and the longer life span of affected cats, it is possible that some of these long-term diabetic complications may be recognized clinically. In part because of their independent nature, diagnostic testing has traditionally been difficult in cats. During the past 5 to 7 years in particular, a great deal of effort has been put forth to validate methods for noninvasive blood pressure measurement in cats, and most investigators agree that the Doppler ultrasonographic technique is an accurate, time- and cost-effective technique. Unfortunately, reliable diastolic blood pressure measurements are difficult to obtain with this technique, and it is possible that some cats in the present study could have been missed.

A major difficulty in definitively diagnosing hypertension involves differentiating transient stress-induced increases in blood pressure (the so-called white coat effect) from true systemic hypertension. For this reason, in the present study, we classified cats as having hypertension only if they had a high systolic blood pressure in conjunction with some other clinical abnormality associated with hypertension. Unlike diabetes mellitus, hypertension can cause predictable, clinically detectable secondary organ damage relatively early in the course of disease. For instance, 80 to 100% of cats also contributes by rendering low-density lipoprotein particles more atherogenic. In the present study, however, there was not a significant correlation between systolic blood pressure and serum fructosamine concentrations in cats with diabetes mellitus.

The possibility of separate classes of diabetes in cats has been suggested, and histologic findings consistent with type I diabetes mellitus have been observed. But in general, diabetes mellitus in cats is not associated with an autoimmune etiology and is associated with obesity, high carbohydrate diets, and increased age, a pattern more typical of type 2 diabetes mellitus in people. It is this ambiguity in classification that, in part, has contributed to the difficulty in identifying the cause of diabetes mellitus in cats. A genetic basis for the development of diabetes has been identified in Burmese cats in Australia and New Zealand, but this is unlikely to explain the high prevalence among mixed-breed cats. It is possible that the cause of diabetes mellitus in cats is sufficiently different from the cause in humans such that affected cats would not have a predilection for hypertension.

It is well documented in humans with diabetes mellitus that the duration of disease and degree of control of hyperglycemia are associated with the risk of developing cardiovascular complications. Similarly, hypertension was associated with the duration of diabetes in a study of 50 dogs with naturally occurring diabetes mellitus. Such an association was not apparent in the 14 diabetic cats in the present study, however. Interestingly, cats do show histologic signs of long-term microvascular diabetic complications, including diabetic retinopathy, nephropathy, and neuropathy. It has been hypothesized that these clinical manifestations of diabetes mellitus are not recognized in cats because of their relatively short life span (2 to 5 years) after the diagnosis of diabetes. In humans, it takes, on average, 15 to 20 years of active diabetes for retinal lesions to develop and 12 to 20 years for nephropathy to develop. With better understanding of the disease and the longer life span of affected cats, it is possible that some of these long-term diabetic complications may be recognized clinically.
with systemic hypertension are reported to have signs of hypertensive retinopathy\cite{17,20,23} that are characterized by intraretinal and subretinal edema, hemorrhage, and detachment.\cite{20,23} These lesions were not identified in any of the 14 diabetic cats evaluated in the present study.

Systemic hypertension commonly induces concentric left ventricular hypertrophy in cats because of increases in cardiac afterload, and in 1 study,\cite{21} 10 of 12 cats with hypertension also had left ventricular hypertrophy. One of 13 cats in the present study had echocardiographic evidence of left ventricular hypertrophy, but systolic blood pressure in this cat was 174 mm Hg, results of an ophthalmologic examination were normal, and serum T₄ concentrations were within reference limits; therefore, a diagnosis of mild hypertrophic cardiomyopathy was made. Four of 13 cats in this study had echocardiographic evidence of left atrial enlargement, but this has not been consistently observed in diabetic cats.\cite{24,25}

Studies of blood pressure between age and blood pressure in the present study. In 1 study,\cite{26} the correlation between age and blood pressure was attributed to an increased likelihood of concurrent subclinical disease with advanced age.

Findings in the present study agree with findings of a previous study\cite{27} in which systemic hypertension was not detected in 10 cats with diabetes mellitus. Together, these results suggest that hypertension does not occur or occurs in only a small percentage of cats with diabetes mellitus. However, additional research with larger numbers of cats is needed to determine whether the degree of glycemic control or duration of disease has an effect on blood pressure in diabetic cats.

References