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OBJECTIVE
To investigate mechanisms by which anti-inflammatory doses of orally administered intermediate-acting glucocorticoids (prednisone) could predispose dogs to progression of heart disease or congestive heart failure.

ANIMALS
11 client-owned dogs with allergic dermatitis and 11 matched control dogs.

PROCEDURES
Clinicopathologic, echocardiographic, and hemodynamic variables were measured. Dogs with allergic dermatitis then received prednisone (1 mg/kg, PO) once daily for 14 consecutive days beginning on day 0 (baseline), followed by a tapering and washout period; control dogs received no treatment. Measurements were repeated on days 7, 14, and 35. Linear mixed modeling was used to compare changes in variables across measurement points and between dog groups.

RESULTS
Prednisone administration caused no significant changes in serum sodium or potassium concentration, blood glucose concentration, or target echocardiographic variables. The change from baseline in systolic arterial blood pressure at day 7 was significantly greater in the prednisone-treated dogs than in control dogs. Expected changes in hematologic and serum biochemical values with prednisone administration (neutrophilia, eosinopenia, isosthenuria, and high serum alkaline phosphatase and alanine aminotransferase activities) also occurred in the prednisone-treated dogs.

CONCLUSIONS AND CLINICAL RELEVANCE
Findings suggested that anti-inflammatory doses of orally administered glucocorticoids have the potential to adversely impact cardiac function in dogs by causing an increase in blood pressure and thus increased cardiac afterload. (*Am J Vet Res* 2018;79:xxx–xxx)

Glucocorticoids are widely used in veterinary medicine for the treatment of many inflammatory, immune-mediated, and neoplastic diseases.[1] However, this use is presently limited for patients with heart disease owing to concern regarding the possible precipitation of CHF.[2,3] Such concern is supported by reports of cats with corticosteroid-associated CHF[4] as well as of humans with Cushingoid-associated CHF.[5,6]

ABBREVIATIONS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
CHF	Congestive heart failure
E:Ea	Early diastolic mitral inflow velocity to early diastolic mitral annular motion
GLS	Global longitudinal strain
IVSd	Interventricular septal thickness at end diastole
LA:Ao	Left atrial diameter to aortic root diameter
LVIDd	Left ventricular internal diameter at end diastole
LVMI	Left ventricular mass index
LVPWd	Left ventricular posterior wall thickness at end diastole
SAP	Systolic arterial blood pressure
USG	Urine specific gravity

The mechanism by which glucocorticoid administration might lead to CHF is not fully understood, but several potential mechanisms have been suggested. These mechanisms include water retention and an increase in total body water content attributable to the mild mineralocorticoid effects of some glucocorticoids[7]; plasma volume expansion resulting from glucocorticoid-induced insulin resistance and hyperglycemia[8]; direct glucocorticoid-induced structural cardiac remodeling, specifically left ventricular hypertrophy and diastolic dysfunction[9]; and increased left ventricular afterload secondary to glucocorticoid-induced vasoconstriction.[10–12]

Despite the theoretical concern that glucocorticoid administration might precipitate CHF, a paucity of data exists regarding any adverse effects of such drugs in patients with heart disease. Other than a case series report[4] of CHF following injection of long-acting glucocorticoids in cats, no primary literature is available to support a contraindication to glucocorticoid administration in patients with heart disease.[2,3] It is even possible that the diuretic effects

of glucocorticoids may be beneficial in patients with CHF.

Results of several experimental studies have suggested that glucocorticoid administration increases renal blood flow and glomerular filtration rate via both direct mechanisms (eg, dopamine, nitric oxide, and vasodilation of afferent arterioles)[13–17] and indirect mechanisms (eg, potentiation of atrial natriuretic peptide).[18–22] These beneficial effects have been investigated in clinical trials[23–26] involving humans with advanced decompensated CHF, showing that prednisone administration can potentiate diuresis, particularly in humans with diuretic resistance, leading to improved clinical outcomes.

To the authors' knowledge, only 1 prospective veterinary study[27] (involving cats) has been conducted to examine the underlying mechanism by which glucocorticoids might exacerbate heart disease. Investigators in that study[27] concluded that the most likely explanation for steroid-induced CHF in cats was transient hyperglycemia causing an intravascular fluid shift. To date, no studies have been conducted to investigate the effects of glucocorticoids on hemodynamic parameters or cardiac structure and function in dogs.

The purpose of the study reported here was to determine whether anti-inflammatory doses of orally administered prednisone would cause clinicopathologic, echocardiographic, or hemodynamic changes in dogs that could exacerbate preexisting heart disease or precipitate CHF in susceptible patients. We hypothesized that oral prednisone administration would have no effect on hemodynamically relevant variables in otherwise healthy dogs with allergic dermatitis.

Materials and Methods

Animals

Two groups of dogs were included in the study. The treated group consisted of client-owned dogs with allergic dermatitis that had been evaluated by a board-certified veterinary dermatologist (DJB) as candidates for a short course of anti-inflammatory prednisone treatment. Each dog in this treated group was matched to an untreated control dog of the same sex, neuter status, age (within 1 year), and body weight (within 10% or 7.5 kg). Exclusion criteria included steroid treatment within the previous 4 weeks; evidence of concurrent systemic disease on initial physical examination, CBC, or serum biochemical analysis; or concurrent treatment with a hemodynamically active drug (eg, diuretic, vasodilator, β-adrenoceptor blocker, or positive inotrope).

An a priori sample size calculation indicated that 10 treated dogs with 10 matched controls would be needed to detect a mean difference in blood glucose concentration of 20 mg/dL between groups, with 80% power and an α value of 0.05. This value of 20 mg/dL (with SD of 5 mg/dL) was chosen on the basis of the reported change in blood glucose concentration following glucocorticoid administration in cats with allergic dermatitis.[27] Eleven dogs were enrolled in the treated group, and 11 matched dogs were enrolled in the control group. The study protocol was approved by the Institutional Animal Care and Use Committee at Iowa State University. Informed consent was obtained from all dog owners before the study began.

Study design

A matched clinical trial design with a 35-day monitoring period was used. Baseline measurements were obtained from dogs in both groups on day 0. After returning home, dogs in the treated group began a 14-day course of prednisone treatment (1 mg/kg, PO, q 24 h in the evening administered by owners).[28] After 14 days, owners were instructed to taper the prednisone dose to 0.5 mg/kg every 24 hours for 3 days and then 0.5 mg/kg every 48 hours for 3 doses and then to discontinue prednisone administration. Dogs in this treated group were allowed to receive systemically or topically administered antimicrobials or medicated shampoos for adjunctive treatment of secondary infections associated with allergic dermatitis if indicated. Control dogs received no steroidal medications of any type throughout the entire 35-day period. Owners were instructed to feed dogs their routine commercial diet between 6:00 AM and 8:00 AM on the days when dogs were brought to the hospital to have measurements performed (days 0, 7, 14, and 35), except for a single dog in the treated group from which food was withheld on the mornings of these study visits.

Diagnostic tests

All dogs on all 4 study visit days received a physical examination, SAP measurement, CBC, serum biochemical analysis, urinalysis, transthoracic echocardiographic examination, and plasma volume calculation. On days 0 and 14 only, measurements of serum insulin-to-glucose concentration ratio and serum fructosamine concentration were obtained and a thoracic radiographic examination was performed for all dogs. On days 0, 14, and 35, plasma prednisone concentration was measured for all dogs in the treated group. Additionally, on days 1 through 4, blood glucose concentration dogs in the treated group was measured with a point-of-care device[a] once daily to detect any short-term changes in this variable.

Dogs were weighed at each visit by use of the same digital scale. Systolic arterial blood pressure was measured with a standard noninvasive Doppler ultrasonic flow method[29] by a trained examiner, who used the same patient positioning and cuff size for each visit. Dogs were allowed to acclimate to the hospital environment for at least 15 minutes prior to blood pressure assessment; a minimum of 4 Doppler readings were obtained and averaged for each visit.

Peripheral venous blood samples were collected from external jugular, lateral saphenous, or cephalic veins by use of 1-inch, 22-gauge needles attached to 6- to 12-mL syringes. For each sample, approximately

2 mL of blood was placed in an EDTA tube, and the remaining blood sample was placed in an additive-free tube. Urine samples were collected via ultrasound-guided cystocentesis by use of 1- to 1.5-inch, 22-gauge needles attached to 6-mL syringes and placed in additive-free tubes. All CBCs, serum biochemical analyses, and urinalyses were performed at the Iowa State University Clinical Pathology Laboratory. Serum insulin and glucose measurements were performed at the Michigan State University Diagnostic Center for Population and Animal Health, and serum fructosamine measurement was performed at a commercial laboratory.[b] Plasma samples were stored at −80°C until batch analysis of prednisone concentration by liquid chromatography–mass spectrometry at the Iowa State University Veterinary Diagnostic Laboratory.[30] Percentage change in plasma volume (%ΔPV) was calculated for each visit following day 0 (d0) as follows[27,31]:

$$\%\Delta PV = ([Hb_{d0}/Hb_{dX}] \times [1 - Hct_{dX}]/[1 - Hct_{d0}]) \times 100\%$$

where Hb represents hemoglobin concentration and dX represents the measurement day of interest (day 7, 14, or 35).

All transthoracic echocardiographic examinations were performed by the same board-certified cardiologist (JLW), who used an ultrasound system[c] coupled to 5- to 12-MHz phased array sector transducers.[d] For these examinations, dogs were positioned in right and left lateral recumbency and transthoracic 2-D, M-mode, spectral Doppler, color flow Doppler, and tissue Doppler echocardiographic examinations were performed with standard methods as described elsewhere.[32–35] A simultaneous lead II ECG was recorded. Echocardiographic images were stored digitally and analyzed with the aid of an integrated image analysis system.[e] Images were measured with digital calipers, and all measurements were averaged over 5 observations of sufficient technical quality.

Images for left ventricular size, wall thickness, and systolic function assessments were obtained from standard right parasternal short-axis and left apical long-axis views. Variables measured in M-mode included left ventricular internal diameter at end systole, LVIDd, left ventricular posterior wall thickness at end systole, LVPWd, interventricular septal thickness at end systole, and IVSd. Left ventricular fractional shortening was calculated by subtracting the left ventricular internal diameter at end systole from LVIDd, dividing the result by LVIDd, and then multiplying this quotient by 100%. Left ventricular end-diastolic and end-systolic volume indices and ejection fraction were determined by use of the modified single-plane Simpson method of disks, with images acquired from the left apical 4-chamber view optimized for the left ventricle.[36] Left atrial size was assessed by measuring left atrial and aortic root diameters in 2-D images in the right parasternal short axis view[37,38] and calculating the LA:Ao ratio.

Transmitral flow[39,40] was recorded by means of pulsed-wave Doppler imaging from the left apical 4- and 3-chamber views to measure peak velocity of early and late diastolic transmitral flows and isovolumic relaxation time, respectively. Pulsed-wave tissue Doppler imaging[39,40] was also performed from the left apical 4-chamber view to record the peak early and late velocities of mitral annulus motion at both the lateral and septal mitral valve annulus positions. Peak early-to-peak late velocities ratio and E:Ea ratio were calculated. The LVMI was calculated as follows[41]:

$$LVMI = ([\{1.04 \times (LVIDd + LVPWd + IVSd)3\} - LVIDd3] \times 0.8 + 0.6)/\text{body surface area}$$

Left ventricular strain assessment by myocardial speckle tracking was performed as previously described.[42,43] High-quality 2-D images of the left ventricle (4-chamber, 2-chamber, and 3-chamber including left ventricular outflow tract) were obtained from left apical views. Images were stored digitally in raw data format. Strain measurements were made with the aid of an on-cart strain software package.[f] For a single cardiac cycle in each view of the left ventricle, user-defined reference points guided the software algorithm to define the region of interest incorporating the entire left ventricular myocardial thickness. The software-defined region of interest was visually inspected and manually adjusted, if needed. The speckle-tracking algorithm of the software was then calculated for the strain and strain rate of each myocardial segment, and GLS was calculated for the entire region of interest.

Three-view thoracic radiographs were also obtained on days 0 and 14, and a vertebral heart score was calculated by use of the right lateral view as described elsewhere.[44]

Statistical analysis

To ensure control dogs had been effectively matched to prednisone-treated dogs, the independent 2-sample *t* test assuming equal variances was performed to compare mean body weight and age between these 2 groups, with the null hypothesis that there was no difference.

Values of outcome variables measured at multiple points were compared by means of a linear mixed model.[g] Parameter estimates were obtained for the mean structure, with maximum likelihood as the estimation method and the containment option for degrees of freedom. The covariates of interest in the model were dog group, time (measurement point), and an interaction between these 2 variables. In the analyses, time was treated as a categorical random variable, with categories of 0, 7, 14, and 35 days. Models with a random intercept were used. For outcomes with only 2 measurement points, multiple linear regression was used to model the differences between day 14 and baseline when model assumptions were met. Mean parameter values and residual mean

square error were estimated. Parameter estimates were used to find model-estimated group means for each outcome variable; these model-estimated group means were used to detect significant interactions with dog group and time. At each measurement point following baseline, the change in the outcome variable from baseline was compared between treatment and control groups. Consequently, for each outcome variable, significance was assessed not on the basis of absolute difference between the 2 groups at each measurement point but rather on whether the change between values at baseline and each measurement point differed between groups.

The paired *t* test was performed to compare baseline blood glucose values with those measured in the treated group on days 1 through 4. For all analyses, values of $P < 0.05$ were considered significant. All data are reported as mean ± SD.

Results

Animals

The treated group of dogs with allergic dermatitis that received prednisone and matched control group of healthy dogs both included 8 spayed females and 3 neutered males. Mean ± SD age of treated dogs was 4.9 ± 3.2 years and of control dogs was 5.2 ± 3.5 years ($P = 0.86$). Mean body weight of treated dogs was 23.3 ± 12.5 kg and of control dogs was 23.3 ± 12.3 kg ($P = 0.98$). No dogs had structural heart disease identified on thoracic radiographs or echocardiograms; the only echocardiographic abnormalities noted were trace tricuspid or pulmonic regurgitation.

Outcome variables

Results for each outcome variable for each group at each measurement point were summarized **(Tables 1–4)**. No significant changes from baseline were detected at days 7, 14, or 35 in blood glucose concentration or serum insulin-to-glucose concentration ratio, either within or between groups (Table 1; **Supplementary Figure S1**, available at avmajournals.avma.org/doi/suppl/10.2460/ajvr.79.4.page). Furthermore, no significant changes in blood glucose concentration were detected during the first 4 days of prednisone treatment. Although values were within reference intervals, the change from baseline in serum fructosamine concentration at day 14 differed significantly ($P = 0.007$) between groups, with the treated group having less of an increase than the control group. There was no significant change from baseline in the mean calculated plasma volume within or between the treated or control groups at day 7 (10.6 ± 12.8% and 8.6 ± 11.9%, respectively), day 14 (17.4 ± 21.2% and 5.1 ± 11.4%, respectively), and day 35 (17.9 ± 21.0% and 10.0 ± 11.2%, respectively).

Groups differed significantly ($P = 0.01$) in the change from baseline in SAP at day 7 (Table 2; **Supplementary Figure S2**, available at avmajournals.avma.org/doi/suppl/10.2460/ajvr.79.4.page). Mean SAP in the treated group at this measurement point increased from baseline by 19 mm Hg, whereas mean SAP in the control group decreased by 5 mm Hg. Groups also differed significantly ($P = 0.02$) in the change in body weight at day 7.

Changes from baseline in some leukogram variables differed significantly between groups (Table 3; **Supplementary Figure S3**, available at avmajournals.avma.org/doi/suppl/10.2460/ajvr.79.4.issue.page). Specifically, neutrophil counts increased in the treated group at both days 7 ($P = 0.046$) and 14 ($P = 0.002$), whereas eosinophil counts decreased in the treated group at days 7 ($P = 0.03$), with values restored to baseline by day 35. Monocyte counts were significantly ($P < 0.001$) higher in the treated group than the control group at all measurement points. Neutrophil counts at days 7 and 14 exceeded the upper reference limit for only 2 treated dogs; other leuk-

Table 1—Mean ± SD values and percentage changes from baseline (day 0, prior to treatment initiation) at various points for glucose metabolism variables for 11 dogs with allergic dermatitis treated with prednisone (1 mg/kg, PO, once daily for 14 days; treated group) and 11 healthy untreated dogs (control group).

Variable, by measurement point	Reference interval	Control group	Change from baseline (%)	Treated group	Change from baseline (%)
Blood glucose (mg/dL)					
Day 0	68–115	100 ± 11	—	101 ± 11	—
Day 7	—	102 ± 13	2.0	103 ± 10	2.0
Day 14	—	100 ± 8	0	98 ± 10	–3.0
Day 35	—	102 ± 10	2.0	101 ± 11	0
Serum insulin-to-glucose concentration ratio					
Day 0	14–43	37 ± 19	—	41 ± 52	—
Day 14	—	44 ± 30	18.9	55 ± 25	34.2
Serum fructosamine (μmol/L)					
Day 0	177–314	201 ± 13	—	212 ± 14	—
Day 14	—	221 ± 19	10.0	216 ± 20	1.9*

*Parameter estimates from linear mixed models indicated a significantly ($P < 0.05$) different change from baseline in the treated group with the control group.

— = Not applicable or already reported.

Table 2—Mean ± SD values and percentage changes from baseline at various points for physiologic variables for the dogs of Table 1.

Variable, by measurement point	Control group	Change from baseline (%)	Treated group	Change from baseline (%)
Body weight (kg)				
Day 0	23.1 ± 12.3	—	23.2 ± 12.5	—
Day 7	23.1 ± 12.2	0	22.6 ± 12.1	–2.6*
Day 14	23.1 ± 12.2	0	22.7 ± 12.3	–2.2
Day 35	23.3 ± 12.4	0.9	23.7 ± 12.8	–2.2
Heart rate (beats/min)				
Day 0	110 ± 27	—	108 ± 17	—
Day 7	117 ± 33	6.4	100 ± 26	–7.4
Day 14	116 ± 28	5.5	95 ± 14	–12.0
Day 35	112 ± 38	1.8	108 ± 23	0
SAP (mm Hg)				
Day 0	152 ± 34	—	148 ± 25	—
Day 7	147 ± 24	–3.3	167 ± 20	12.8*
Day 14	145 ± 19	–4.6	156 ± 20	5.4
Day 35	141 ± 17	–7.2	134 ± 24	–9.5

See Table 1 for remainder of key.

ogram changes occurred within the respective reference intervals. No significant differences between or within groups were detected in blood hemoglobin concentration, Hct, or platelet count.

Changes from baseline in several serum biochemical variables differed significantly between groups (Table 3; Supplementary Figure S3). Serum ALP activity increased significantly from baseline in the treated group versus the control group at both days 7 ($P = 0.04$) and 14 ($P = 0.003$), whereas such an increase was evident in serum ALT activity at day 14 only ($P = 0.01$). The decrease in serum cholesterol concentration in the treated group was significantly different from the value in the control group at days 14 ($P = 0.01$) and 35 ($P = 0.02$), with no significant decrease from baseline at day 7. Changes from baseline in serum total protein concentration differed significantly between groups at days 7 ($P < 0.001$) and 35 ($P = 0.04$), whereas changes in serum albumin concentration were significantly greater in the treated group than in the control group at day 7 ($P < 0.001$) and 14 ($P = 0.004$). Additionally, compared with changes from baseline in the control group, treated-group values for serum chloride concentration decreased from baseline at both days 7 and 14 ($P < 0.001$), serum creatinine concentration decreased from baseline at both days 7 ($P = 0.0011$) and 14 ($P < 0.001$), and serum magnesium concentration increased from baseline at both days 7 ($P < 0.001$) and 14 ($P = 0.005$). Of these changes, only values of 3 serum biochemical variables increased (ALP and ALT activities) or decreased (chloride concentration) relative to respective reference limits. No significant changes were detected in serum sodium or potassium concentration at any measurement point.

Changes from baseline in both USG and urine pH differed significantly between groups (Table 3; Supplementary Figure S3). Specifically, USG in the treated group decreased from baseline at day 14 ($P < 0.001$), whereas urine pH decreased at days 7 ($P = 0.008$), 14 ($P < 0.001$), and 35 ($P = 0.005$). Owner-assessed water intake and urine output were reportedly increased in prednisone-treated dogs by day 7. Plasma prednisone concentration was undetectable in all treated dogs at days 0 and 35. After 14 days of prednisone treatment, median plasma prednisone concentration was 1.78 ng/mL (95% confidence interval, < 0.2 to 12.4 ng/mL).

Changes from baseline in 3 echocardiographic variables targeted for analysis differed significantly between the treatment and control groups: LVIDd, GLS, and E:Ea (Table 4; **Supplementary Figure S4**, available at avmajournals.avma.org/doi/suppl/10.2460/ajvr.79.4.page). Specifically, LVIDd increased from baseline in the treated group at days 7 ($P = 0.04$) and 14 ($P = 0.01$), whereas GLS decreased (became more negative, indicating improved function) in the treated group at days 7 ($P = 0.02$) and 14 ($P = 0.008$). The E:Ea ratio increased from baseline in the treated group at day 35 ($P = 0.01$). No echocardiographic variables were outside reference intervals at any measurement point. No changes from baseline were identified in measurements of left ventricular wall thickness, left atrial size, left ventricular systolic function, or radiographic vertebral heart score. All thoracic radiographs where interpreted as unremarkable at all points.

Discussion

The purpose of the study reported here was to investigate the effects of anti-inflammatory doses of prednisone in dogs, with the goal of detecting any clinicopathologic, hemodynamic, or echocardiographic changes that might have potential to precipitate CHF (particularly in dogs with preexisting heart disease). Only 2 previous veterinary studies (both involving cats) have been reported regarding the potential of glucocorticoid treatment to exacerbate heart disease. The first study[4] was a case series of 12 otherwise healthy cats with allergic dermatitis that developed acute CHF

Table 3—Mean ± SD values and percentage change from baseline at various points for selected CBC, serum biochemical, and urinalysis variables for the dogs of Table 1.

Variable, by measurement point	Reference interval	Control group	Change from baseline (%)	Treated group	Change from baseline (%)
Hemoglobin (g/dL)					
Day 0	12–18	17.0 ± 2.1	—	17.1 ± 1.5	—
Day 7	—	16.4 ± 2.1	–3.5	16.3 ± 1.5	–4.7
Day 14	—	16.7 ± 2.1	–1.8	15.7 ± 1.4	–8.2
Day 35	—	16.5 ± 2.3	–2.9	17.5 ± 6.4	2.3
Hct (%)					
Day 0	37–55	51.2 ± 5.9	—	50.6 ± 4.4	—
Day 7	—	49.1 ± 6.0	–4.1	48.4 ± 4.6	–4.4
Day 14	—	49.1 ± 6.2	–4.1	43.7 ± 14.9	–13.6
Day 35	—	48.0 ± 6.9	–6.3	46.9 ± 5.9	–7.3
Platelets (X 10^3/L)					
Day 0	200–500	262 ± 69	—	257 ± 145	—
Day 7	—	249 ± 61	–5.0	294 ± 140	14.4
Day 14	—	259 ± 78	–1.2	299 ± 93	16.3
Day 35	—	248 ± 77	–5.3	242 ± 159	–5.8
Neutrophils (X 10^3/μL)					
Day 0	3.0–11.4	5.10 ± 1.62	—	5.72 ± 1.75	—
Day 7	—	5.43 ± 1.99	6.5	8.18 ± 2.83	43.0*
Day 14	—	4.35 ± 1.84	–14.7	8.47 ± 3.00	48.1*
Day 35	—	4.30 ± 1.41	–15.7	4.71 ± 1.27	–17.7
Lymphocytes (X 10^3/μL)					
Day 0	1.0–4.8	1.75 ± 0.69	—	1.92 ± 0.87	—
Day 7	—	1.76 ± 0.83	0.6	1.59 ± 0.96	–17.2
Day 14	—	1.92 ± 0.96	9.7	1.69 ± 1.28	–12.0
Day 35	—	1.76 ± 1.00	0.6	1.90 ± 1.02	–1.0
Monocytes (X 10^3/μL)					
Day 0	0.15–1.35	0.36 ± 0.19	—	0.45 ± 0.30	—
Day 7	—	0.36 ± 0.21	0	0.66 ± 0.41	46.7
Day 14	—	0.26 ± 0.18	–27.8	0.55 ± 0.13	22.2
Day 35	—	0.24 ± 0.14	–33.3	0.42 ± 0.27	–6.7
Eosinophils (X 10^3/μL)					
Day 0	0–0.75	0.40 ± 0.25	—	0.41 ± 0.28	—
Day 7	—	0.47 ± 0.52	17.5	0.14 ± 0.26	–65.9*
Day 14	—	0.28 ± 0.11	–30.0	0.14 ± 0.17	–65.9
Day 35	—	0.43 ± 0.13	7.5	0.31 ± 0.20	–24.4
Sodium (mEq/L)					
Day 0	141–151	146 ± 2	—	146 ± 3	—
Day 7	—	146 ± 2	0	146 ± 3	0
Day 14	—	147 ± 2	0.7	148 ± 3	1.4
Day 35	—	147 ± 2	0.7	147 ± 3	0.7
Potassium (mEq/L)					
Day 0	3.9–5.3	4.5 ± 0.3	—	4.4 ± 0.6	—
Day 7	—	4.5 ± 0.4	0	4.5 ± 0.7	2.3
Day 14	—	4.4 ± 0.3	–2.2	4.4 ± 0.4	0
Day 35	—	4.5 ± 0.3	0	4.4 ± 0.4	0
Chloride (mEq/L)					
Day 0	112–121	115 ± 2	—	114 ± 2	—
Day 7	—	116 ± 2	0.9	108 ± 3	–5.3*
Day 14	—	115 ± 2	0	109 ± 3	–4.4*
Day 35	—	115 ± 2	0	114 ± 3	0
Bicarbonate (mEq/L)					
Day 0	19–25	23 ± 2	—	23 ± 2	—
Day 7	—	23 ± 2	0	25 ± 3	8.7
Day 14	—	23 ± 3	0	23 ± 2	0
Day 35	—	23 ± 2	0	24 ± 1	4.4
Calcium (mg/dL)					
Day 0	9.7–11.3	10.6 ± 0.4	—	10.6 ± 0.4	—
Day 7	—	10.6 ± 0.5	0	10.6 ± 2.5	0
Day 14	—	10.6 ± 0.4	0	10.6 ± 0.5	0
Day 35	—	10.5 ± 0.4	–0.9	10.6 ± 0.9	0
Phosphorus (mg/dL)					
Day 0	3.2–6.0	3.8 ± 0.7	—	3.7 ± 0.9	—
Day 7	—	3.9 ± 1.0	2.6	4.5 ± 0.5	21.6
Day 14	—	3.9 ± 0.6	2.6	4.2 ± 0.5	13.5
Day 35	—	3.9 ± 0.6	2.6	4.0 ± 0.6	8.1

Table 3 continues on the next page

Variable, by measurement point	Reference interval	Control group	Change from baseline (%)	Treated group	Change from baseline (%)
Magnesium (mg/dL)					
Day 0	1.7–2.5	2.1 ± 0.2	—	2.0 ± 0.2	—
Day 7	—	2.1 ± 0.2	0	2.2 ± 0.1	10.0*
Day 14	—	2.1 ± 0.2	0	2.1 ± 0.1	5.0*
Day 35	—	2.1 ± 0.2	0	2.0 ± 0.1	0
BUN (mg/dL)					
Day 0	10–30	16 ± 4	—	15 ± 5	—
Day 7	—	16 ± 4	0	16 ± 6	6.7
Day 14	—	16 ± 5	0	17 ± 7	13.3
Day 35	—	16 ± 4	0	16 ± 8	6.7
Creatinine (mg/dL)					
Day 0	0.5–1.5	1.1 ± 0.1	—	1.1 ± 0.3	—
Day 7	—	1.1 ± 0.1	0	0.9 ± 0.2	–18.2*
Day 14	—	1.1 ± 0.2	0	0.9 ± 0.3	–18.2*
Day 35	—	1.1 ± 0.2	0	1.0 ± 3	–9.1
Total protein (g/dL)					
Day 0	5.2–7.1	6.2 ± 0.4	—	6.2 ± 0.6	—
Day 7	—	6.1 ± 0.4	–1.6	6.6 ± 0.4	6.5*
Day 14	—	6.3 ± 0.4	1.6	6.4 ± 0.4	3.2
Day 35	—	6.3 ± 0.5	1.6	6.1 ± 0.6	–1.6*
Albumin (g/dL)					
Day 0	2.7–4.0	3.4 ± 0.3	—	3.4 ± 0.3	—
Day 7	—	3.3 ± 0.3	–2.9	3.8 ± 0.2	11.8*
Day 14	—	3.5 ± 0.3	2.9	3.7 ± 0.3	8.8*
Day 35	—	3.4 ± 0.4	0	3.3 ± 0.4	–2.9
ALP (U/L)					
Day 0	20–150	61 ± 46	—	67 ± 80	
Day 7	—	62 ± 45	1.6	143 ± 188	113.4*
Day 14	—	64 ± 45	4.9	180 ± 282	168.7*
Day 35	—	60 ± 37	–1.6	83 ± 140	23.9
ALT (U/L)					
Day 0	24–90	55 ± 20	—	55 ± 15	—
Day 7	—	52 ±19	–5.5	57 ± 14	3.6
Day 14	—	53 ± 18	–3.6	74 ± 36	34.6*
Day 35	—	52 ± 18	–5.5	48 ± 17	–12.7
Cholesterol (mg/dL)					
Day 0	132–300	231 ± 47	—	224 ± 46	—
Day 7	—	230 ± 58	–0.4	218 ± 46	–2.7
Day 14	—	245 ± 55	6.1	205 ± 42	–8.5*
Day 35	—	246 ± 57	6.5	208 ± 42	–7.1*
Triglycerides (mg/dL)					
Day 0	24–115	76 ± 42	—	114 ± 155	—
Day 7	—	92 ± 41	21.1	119 ± 78	4.4
Day 14	—	89 ± 62	17.1	121 ± 108	6.1
Day 35	—	99 ± 78	30.3	92 ± 74	–19.3
USG					
Day 0	1.015–1.045	1.034 ± 0.008	—	1.029 ± 0.016	
Day 7	—	1.031 ± 0.013	–0.3	1.024 ± 0.017	–0.5
Day 14	—	1.034 ± 0.012	0	1.011 ± 0.007	–1.8*
Day 35	—	1.032 ± 0.012	–0.2	1.028 ± 0.018	–0.10
Urine pH					
Day 0	5.5–8.5	6.8 ± 0.8	—	7.8 ± 0.4	—
Day 7	—	7.5 ± 1.0	10.3	7.1 ± 0.9	–9.0*
Day 14	—	7.6 ± 0.8	11.8	6.9 ± 0.6	–11.5*
Day 35	—	7.4 ± 0.9	8.8	7.2 ± 0.8	–7.7*

See Table 1 for remainder of key.

after receiving parenterally administered long-acting methylprednisolone acetate. In the cats that survived the initial CHF episode, serial echocardiography revealed resolution of cardiac abnormalities, and all CHF medications were eventually discontinued. The second study,[27] which was a prospective clinical trial conducted by the same research group, involved evaluation of the effects of anti-inflammatory doses of injectable long-acting methylprednisolone acetate in systemically healthy cats with dermatologic disease, similar to the dogs of the present study. These cats had no changes in blood pressure, echocardiographic variables, total body water content, body weight, or serum sodium-to-potassium concentration ratio at either of 2 measurement points (3 to 6 days and 16 to 24 days following glucocorticoid administration). However, significant and clinically relevant hyperglycemia (mean blood glucose concentration, 187 mg/dL) and high plasma volume were reported 3 to 6 days following glucocorticoid administration. These findings suggested that a

Table 4—Mean ± SD values and percentage change from baseline at various points for selected echocardiographic and radiographic variables for the dogs of Table 1.

Variable, by measurement point	Reference interval	Control group	Change from baseline (%)	Treated group	Change from baseline (%)
IVSd (cm)					
Day 0	0.62 to 1.26	0.90 ± 0.16	—	0.90 ± 0.22	—
Day 7	—	0.95 ± 0.22	5.6	0.91 ± 0.19	1.1
Day 14	—	0.96 ± 0.22	6.7	0.91 ± 0.18	1.1
Day 35	—	0.86 ± 0.16	–4.4	0.96 ± 0.18	6.7
LVIDd (cm)					
Day 0	3.19 to 4.65	3.78 ± 1.05	—	3.62 ± 0.65	—
Day 7	—	3.74 ± 1.06	–1.1	3.79 ± 0.76	4.7*
Day 14	—	3.73 ± 0.99	–1.3	3.85 ± 0.87	6.4*
Day 35	—	3.73 ± 1.17	–1.3	3.62 ± 0.68	0
LVPWd (cm)					
Day 0	0.60 to 1.24	0.85 ± 0.18	—	0.83 ± 0.20	—
Day 7	—	0.88 ± 0.16	3.5	0.82 ± 0.15	–1.2
Day 14	—	0.91 ± 0.20	7.1	0.81 ± 0.13	–2.4
Day 35	—	0.86 ± 0.17	1.2	0.88 ± 0.20	6.0
Fractional shortening (%)					
Day 0	33–45	35.8 ± 7.5	—	32.1 ± 3.8	—
Day 7	—	36.7 ± 10.1	2.5	31.0 ± 4.4	–3.4
Day 14	—	36.7 ± 9.4	2.5	31.5 ± 4.3	–1.9
Day 35	—	34.4 ± 6.7	–3.9	33.0 ± 5.7	2.8
LA:Ao ratio					
Day 0	0.84 to 1.27	1.15 ± 0.11	—	1.22 ± 0.08	—
Day 7	—	1.18 ± 0.12	2.6	1.16 ± 0.07	–4.9
Day 14	—	1.11 ± 0.09	–3.5	1.16 ± 0.10	–4.9
Day 35	—	1.19 ± 0.09	3.5	1.18 ± 0.11	–3.3
E:A ratio					
Day 0	0.93 to 1.98	1.48 ± 0.59	—	1.40 ± 0.34	—
Day 7	—	1.46 ± 0.40	–1.4	1.60 ± 0.35	14.3
Day 14	—	1.49 ± 0.38	0.7	1.60 ± 0.33	14.3
Day 35	—	1.50 ± 0.49	1.4	1.50 ± 0.41	7.1
E:IVRT ratio					
Day 0	0.39 to 1.01	1.27 ± 0.35	—	1.11 ± 0.32	—
Day 7	—	1.18 ± 0.37	–7.1	1.17 ± 0.33	5.4
Day 14	—	1.19 ± 0.41	–6.3	1.18 ± 0.42	6.3
Day 35	—	1.08 ± 0.32	–15.0	1.13 ± 0.28	1.8
E:Ea ratio					
Day 0	6.5 to 10.8	9.39 ± 2.57	—	6.73 ± 1.69	—
Day 7	—	9.53 ± 2.07	1.5	7.74 ± 3.05	15.0
Day 14	—	8.97 ± 1.91	–4.5	6.71 ± 1.88	–0.3
Day 35	—	8.30 ± 2.17	–11.6	7.87 ± 2.53	16.9*
GLS (%)					
Day 0	–11 to –21	–21.6 ± 3.1	—	–18.6 ± 3.1	—
Day 7	—	–20.7 ± 3.1	–4.2	–21.4 ± 3.4	15.1*
Day 14	—	–20.3 ± 4.3	–6.0	–20.8 ± 3.1	11.8*
Day 35	—	–20.8 ± 4.0	–3.7	–18.7 ± 4.1	0.5
LVEF (%)					
Day 0	52 to 67	59.0 ± 12.9	—	56.8 ± 7.5	—
Day 7	—	59.5 ± 9.3	0.9	59.5 ± 7.6	4.8
Day 14	—	60.3 ± 9.8	2.2	61.1 ± 6.9	7.6
Day 35	—	58.3 ± 8.2	–1.2	58.1 ± 7.1	2.3
LVMI (g/m^2)					
Day 0	24.2 to 189.2	129.53 ± 34.69	—	119.35 ± 32.00	—
Day 7	—	136.78 ± 40.87	5.6	132.51 ± 39.62	11.0
Day 14	—	140.54 ± 37.57	8.5	132.19 ± 35.28	10.8
Day 35	—	124.08 ± 37.19	–4.2	128.93 ± 35.83	8.0
Vertebral heart score					
Day 0	9.2 to 10.2	10.24 ± 0.53	—	10.35 ± 0.66	—
Day 7	—	10.24 ± 0.61	0	10.32 ± 0.61	–0.3

E:IVRT ratio = Ratio of early diastolic transmitral flow velocity to IVRT. LVEF = Left ventricular ejection fraction.

plausible mechanism for glucocorticoid-induced CHF in cats was transient hyperglycemia causing an intravascular fluid shift.

No analogous studies have been reported regarding the effects of glucocorticoid administration on fluid balance in dogs. Because long-term anti-inflammatory doses of orally administered prednisone in healthy dogs are not known to result in hyperglycemia or insulin resistance,[45–47] we hypothesized that short-term oral prednisone administration in the enrolled

systemically healthy dogs would cause no clinically relevant hyperglycemia or changes in intravascular volume sufficient to precipitate CHF. Furthermore, we hypothesized that short-term anti-inflammatory prednisone treatment would yield no hemodynamic changes that could precipitate CHF by other mechanisms, including mineralocorticoid effects, structural cardiac abnormalities, or altered blood pressure.

Results supported our first hypothesis that anti-inflammatory doses of orally administered prednisone do not exert acute diabetogenic effects that lead to an increase in plasma volume in dogs, contrary to previous findings in cats.[27] No significant change from baseline was identified in blood glucose concentration at any measurement point, including short-term blood glucose measurements on days 1 through 4 of prednisone treatment. Additionally, no change in the insulin-to-glucose concentration ratio was detected in prednisone-treated dogs. Interestingly, the change from baseline in serum fructosamine concentration at day 14 differed significantly between prednisone-treated and control dogs because of a larger increase in mean serum fructosamine concentration in the control group (from 201 to 221 µmol/L) versus the treated group (from 212 to 216 µmol/L). Although this difference was significant, serum fructosamine concentration remained within the established reference interval, suggesting that this result was likely clinically unimportant and due to random chance. Finally, prednisone-treated dogs had no increases in plasma volume, compared with percentage changes in control dogs, although there was notable variation in calculated plasma volume in both groups. The lack of an increase in blood glucose concentration for dogs with allergic dermatitis receiving anti-inflammatory doses of prednisone suggested that, unlike in cats, plasma volume expansion resulting from insulin resistance and hyperglycemia was not an important risk of glucocorticoid administration in dogs.

The present study yielded no evidence of mineralocorticoid effect in prednisone-treated dogs, supporting the second aspect of our hypothesis. No significant changes in serum sodium or potassium concentration were detected in the treated group relative to the changes in the control group at any measurement point. Although other downstream mineralocorticoid effects were not assessed,[48,49] our findings supported the finding in cats[27] that sodium retention and an increase in total body water content are not clinically important consequences of prednisone administration at anti-inflammatory doses.

Exposure to chronically high endogenous glucocorticoid concentrations reportedly causes direct cardiac remodeling in patients with hyperadrenocorticism. Echocardiographic changes, particularly concentric left ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction, are common in people with hyperadrenocorticism, and Cushingoid patients are at increased risk of adverse cardiovascular outcomes such as myocardial infarction and stroke.[6,50,51] Cardiac changes have also been reported for dogs with hyperadrenocorticism; in a case series[9] of 22 Cushingoid dogs, 68% had mild increases in left ventricular wall thickness. In both humans and dogs, there is no consistent correlation between left ventricular wall thickness and SAP, suggesting that cardiac remodeling in hyperadrenocorticism is independent of the hemodynamic effects of systemic hypertension that often accompanies hyperadrenocorticism.

Although mild echocardiographic abnormalities may be fairly common in Cushingoid dogs, the clinical relevance of such changes is unclear. From a clinical perspective, hyperadrenocorticism in dogs is not generally considered to be a risk factor for the presence or more rapid progression of common heart diseases, such as degenerative mitral valve disease or dilated cardiomyopathy. If chronic endogenous hypercortisolemia causes only mild echocardiographic effects, we would not expect considerable cardiac remodeling with short-term exogenous glucocorticoid administration. Nonetheless, given the potential for a direct glucocorticoid effect on myocardial structure and function, we evaluated serial echocardiographic findings in dogs receiving short-term prednisone treatment. All indices of left ventricular myocardial thickness (LVPWd, IVSd, and LVMI) were unchanged in prednisone-treated dogs, as were indices of left ventricular systolic (fractional shortening) and diastolic (ratio of early to late diastolic transmitral flow velocity) function. Of all echocardiographic variables analyzed, only 3 had changes from baseline that differed significantly between prednisone-treated and control dogs (LVIDd, E:Ea ratio, and GLS). The magnitude of these changes was small, and no echocardiographic measurements fell outside reference intervals at any measurement point. Findings therefore supported the third aspect of our hypothesis, that no clinically relevant changes in cardiac structure or function would occur in dogs receiving anti-inflammatory prednisone treatment.

The most interesting result of the study reported here was that, contrary to the fourth aspect of our hypothesis (and contrary to findings in cats receiving long-acting injectable methylprednisolone acetate), SAP significantly increased from baseline in the prednisone-treated dogs at day 7, compared with the change from baseline in the control group. The magnitude of this increase was both significant and clinically important: from baseline to day 7, mean SAP in treated dogs increased approximately 13%, from 148 to 167 mm Hg, and crossed the threshold for the definition of systemic hypertension in dogs.[52] Although such a change would unlikely be clinically relevant in a healthy dog, it is conceivable that an increase in blood pressure of this magnitude could exacerbate preexisting heart disease via an increase in left ventricular afterload. Systemic hypertension is known to cause secondary structural and functional cardiac abnormalities, specifically concentric left ven-

tricular hypertrophy, dilation of the ascending aorta, coronary artery ischemia, and LV diastolic dysfunction.[53,54] Furthermore, an increase in afterload worsens mitral regurgitation volume, which could lead to a critical increase in left atrial pressure in a dog with advanced degenerative mitral valve disease.[55]

Given the findings of the present study, we suggest that if glucocorticoids can precipitate CHF in susceptible dogs, a plausible mechanism could be glucocorticoid-induced vasoconstriction and development of systemic hypertension. Possible mechanisms for this short-term glucocorticoid-associated increase in SAP include mild mineralocorticoid effects causing sodium retention and increasing circulating volume[7] (which is unlikely owing to the lack of significant changes in sodium or potassium in the prednisone-treated dogs), activation of the renin-angiotensin-aldosterone system,[56-58,h] enhanced vascular system sensitivity to endogenous catecholamines,[56,59,60] suppression of endogenous vasodilatory systems or upregulation of endogenous vasoconstrictor systems,[56,61,i,j] afferent renal arteriole sclerosis and glomerular ischemia resulting in glomerulosclerosis,[62] or a combination of these mechanisms. Depending on the duration of glucocorticoid administration, long-term complications of this glucocorticoid-associated increase in SAP may occur as well. Chronic increases in peripheral vascular resistance can lead to vascular remodeling, further increasing vascular resistance and hypertension.[63,64] Additional investigation is warranted to explore mechanisms of blood pressure regulation in dogs receiving glucocorticoids (both short-term and long-term treatment), particularly given that some mechanisms could be manipulated pharmacologically to mitigate glucocorticoid-induced systemic hypertension.

Systolic arterial blood pressure also increased from baseline in the prednisone-treated group at day 14, but this change was not significant. By day 35, SAP in this group had returned to baseline (mean ± SD, 134 ± 24 mm Hg), suggesting that glucocorticoid-induced changes in SAP resolved following prednisone washout. Potential explanations for the decrease in SAP in the prednisone-treated dogs between days 7 and 14 could have included dogs becoming more acclimated to blood pressure measurements by the third study visit or long-term physiologic reflexes and neurohormonal systems compensating for glucocorticoid-induced vasoconstriction.[65] Interestingly, a nonsignificant decrease in heart rate occurred in prednisone-treated versus control dogs throughout treatment; mean heart rate in the treated group decreased from 108 beats/min at baseline to 100 beats/min at day 7 and 95 beats/min at day 14. It was therefore possible that over time, a baroreceptor-induced decrease in heart rate could have compensated for the glucocorticoid-induced increase in systemic vascular resistance such that SAP in the treated group was normalizing by day 14. It remains unknown whether and how quickly blood pressure in the treated group might have normalized had prednisone administration been continued beyond 14 days (plus washout), but these questions deserve further investigation.

Not surprisingly, prednisone-treated dogs in the present study also had many expected glucocorticoid-associated changes evident on CBC, serum biochemical analysis, and urinalysis. Both neutrophil count and eosinophil count increased in the treated group and returned to baseline values by day 35.[66,67] Interestingly, monocyte counts were higher in the treated versus control group at all measurement points, instead of the expected increase in monocyte count during glucocorticoid administration only[63]; this higher monocyte count may have reflected mild chronic inflammation in dogs with dermatologic disease.[66] Serum biochemical analyses of the prednisone-treated dogs revealed several changes known to be associated with glucocorticoid treatment, including high ALP and ALT activities,[66,68,69] low chloride concentration reportedly due to glucocorticoid stimulation of endogenous organic acid production and renal tubular secretion of hydrogen (and accompanying chloride) ions,[70,71] and high albumin and total protein concentrations believed to be due to increases in the production and lifespan of albumin.[66,67,72] All biochemical values in treated dogs returned to baseline by day 35.

Urinalysis of prednisone-treated dogs revealed a decrease in USG, likely owing to a decrease in the secretion of antidiuretic hormone[73–75] and other steroid-induced mechanisms of diuresis,[76,77] as well as a decrease in urine pH throughout treatment, likely due to an increase in tubular hydrogen ion secretion. Although mean USG decreased significantly in treated dogs only at day 14, 8 of those 11 dogs had a decrease in USG by day 7, with 4 of these dogs becoming isosthenuric by that time. In addition to these objective changes in urine production, subjective (owner-reported) increases in water intake and urine output occurred in all prednisone-treated dogs during treatment. These glucocorticoid-associated changes have all been documented previously, and none are likely to contribute to progression of heart disease or precipitation of CHF.

The present study also revealed several surprising, but likely incidental, changes in outcome variables for prednisone-treated versus control dogs. First, serum cholesterol concentration significantly decreased from baseline in the treated group at days 14 and 35, which was unexpected given that prednisone treatment might be expected to increase serum cholesterol concentration.[66] However, all cholesterol values remained within reference intervals, and no diet standardization was enforced for participating client-owned dogs, complicating the interpretation of these results. In addition, serum creatinine concentration decreased from baseline in the treated group at days 7 and 14. Although this may have represented a clinically irrelevant finding because all creatinine values remained well within the reference interval, possible explanations for the decrease could include

a glucocorticoid-mediated increase in glomerular filtration rate or steroid-induced muscle wasting. Finally, body weight significantly decreased from baseline in the treated group at day 7. Possible glucocorticoid-associated mechanisms for this decrease included dehydration from steroid-induced polyuria (although USG was not significantly decreased at this point and no dogs had signs of clinical dehydration on physical examination), glucocorticoid-induced loss of muscle mass (possibly supported by the decrease in creatinine at days 7 and 14), or both.

The present study had several limitations. First, the sample size calculated was based on blood glucose concentration findings in a previous cat study.[27] A second limitation related to the timing of study visits. Maximal plasma concentration of prednisolone, the active metabolite of prednisone, occurs approximately 30 minutes after a prednisone dose is orally administered (for an immediate-release formulation), and the elimination half-life of prednisolone has been reported to be approximately 1.4 hours.[78,79] In the study reported here, prednisone was administered in the evening and all study visits occurred in the morning. Therefore, none of the measurement points allowed testing of dogs at the time of maximal plasma prednisone concentration, and both day 7 and day 14 visits occurred after dogs had achieved a pharmacokinetic steady state. However, many of the clinical effects of glucocorticoids are genomic effects that become apparent only after 3 to 4 days,[80] making the timing of a pharmacodynamic steady-state difficult to predict. Measurement timings were chosen to capture not only the maximal cumulative glucocorticoid effect (presumably both pharmacokinetic and pharmacodynamic steady-state) at day 14, but also potential earlier, nongenomic glucocorticoid effects mediated by cytosolic or membrane-bound glucocorticoid receptors (such as those observed 3 to 7 days following injection of long-acting methylprednisolone acetate in cats).[27] We acknowledge that by choosing this schedule of study visits, we may have missed glucocorticoid effects that were dependent on peak plasma prednisolone concentrations.

A third limitation of the present study was that only the effects of short-term prednisone administration (14 days plus tapering period) were investigated. Long-term glucocorticoid exposure might have led to different or more significant cardiovascular changes; therefore, data from this study cannot necessarily be extrapolated to long-term glucocorticoid administration, as commonly used for dogs with chronic inflammatory or immune-mediated diseases. A fourth major limitation was that the study dogs had no clinical or echocardiographic evidence of cardiac disease. Healthy dogs were chosen as a logical first step in investigating the cardiovascular effects of glucocorticoids in dogs, analogous to previous work in cats.[27] Additional studies are needed to determine whether clinicopathologic, echocardiographic, or hemodynamic effects of anti-inflammatory prednisone treatment may be different in dogs with underlying heart disease and whether such changes may cause clinically relevant disease progression or possibly precipitate CHF.

A fifth limitation was that dogs were not acclimated to the hospital environment prior to the first study visit, which may have resulted in falsely high blood pressure readings (the so-called white-coat effect). In a study[65] of repeated Doppler blood pressure measurements in untrained Beagles, mean arterial blood pressure progressively decreased over the first 4 measurements before reaching a plateau with acclimation. Because dogs in the treated group were client owned and had allergic dermatitis requiring glucocorticoid treatment, it was not feasible to arrange multiple acclimation visits before beginning the study. Furthermore, inclusion of a control group (in which SAP was observed to decrease slightly with progressive visits) supported that the spike in SAP in the treated group at day 7 was associated with prednisone administration rather than anxiety from repeated hospital visits. A sixth limitation was that investigators were not blinded to treatment group, which could have introduced bias in blood pressure or echocardiographic measurements. Yet another limitation was that no measurement was performed of cardiac biomarkers (eg, cardiac troponin I or N-terminal pro–B-type natriuretic peptide), indices of adrenal function (including serum cortisol concentration), or markers of renin-angiotensin-aldosterone system activity. Evaluation of such parameters may have provided additional information about cardiovascular changes during prednisone treatment.

Overall, the present study revealed that otherwise healthy dogs with allergic dermatitis given anti-inflammatory doses of orally administered prednisone for 14 consecutive days had a modest increase in SAP, but no significant changes in blood glucose concentration, serum sodium or potassium concentration, or echocardiographic indices of wall thickness or cardiac function. No evidence was obtained to support the concern that anti-inflammatory doses of orally administered glucocorticoids cause hyperglycemia or plasma volume expansion in dogs. Instead, our findings suggested that if glucocorticoid use is associated with exacerbation or precipitation of CHF in susceptible dogs, increased left ventricular afterload is a plausible mechanism.

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Footnotes

a. AlphaTRAK 2, Zoetis, Parsippany, NJ.
b. IDEXX Laboratories Inc, Westbrook, Me.
c. Epiq 7C Ultrasound System, Philips Healthcare, Andover, Mass.
d. FUS8350 X5-1, FUS8392 S8-3, and FUS8393 S12-4 transducers, Philips Healthcare, Andover, Mass.
e. Syngo Dynamics, Siemens Medical Solutions, Malvern, Pa.
f. QLAB 10, Philips Healthcare, Andover, Mass.
g. PROC MIXED, SAS, version 9.4, SAS Institute Inc, Cary, NC.
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