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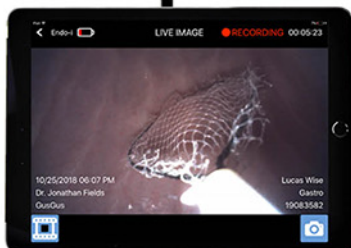
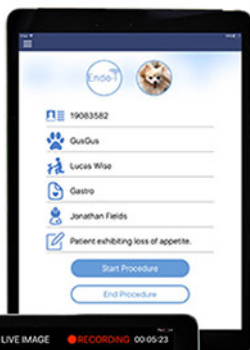
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STANDARD ARTICLE

Prevalence and risk factors associated with systemic hypertension in dogs with spontaneous hyperadrenocorticism

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Abstract

Background: Systemic hypertension (SH) is common in dogs with hyperadrenocorticism (HAC) however there are not many studies assessing its prevalence and risk factors.

Objectives: To determine the prevalence and severity of SH in dogs with HAC and its association with clinical and laboratory findings to identify potential risk factors.

Animals: Sixty-six client owned dogs with spontaneous HAC.

Methods: Retrospective cross-sectional study. Medical records of dogs with HAC were reviewed. Systolic blood pressure (SBP) was measured using Doppler ultrasonography. Clinical signs, physical examination findings and clinicopathologic data (CBC, serum biochemistry and electrolytes, urinalysis and urinary culture, and adrenal function tests) were reviewed for analysis.

Results: Prevalence of SH (≥ 150 mm Hg) was 82% (54/66) and prevalence of severe SH (≥ 180 mm Hg) was 46% (30/66). All dogs with thrombocytosis had SH ($P = .002$), and a platelet count $\geq 438 \times 10^3/\mu\text{L}$ was 100% specific and 61.1% sensitive to predict SH (AUC = .802, $P = .001$). Median potassium levels were lower in hypertensive dogs (4.1 mEq/L, range 3.1–5.4 mEq/L) than in normotensive ones (4.5 mEq/L, range 4.0–5.0 mEq/L) ($P = .007$). Dogs with UPC ≥ 0.5 had higher median SBP than those without proteinuria ($P = .03$). Dogs with concurrent diabetes mellitus seemed to have a reduced risk of SH (OR = .118, 95%CI = .022–.626, $P = .02$).

Conclusions and Clinical Importance: Systemic hypertension is common in dogs with HAC and is frequently severe. Blood pressure should be routinely assessed in these dogs, especially if thrombocytosis, proteinuria or low potassium concentrations are present.

KEYWORDS

blood pressure, canine, cortisol, Cushing, hypercortisolism

Abbreviations: 11 β -HSD, 11 β -hydroxysteroid dehydrogenase; ADH, adrenal-dependent hyperadrenocorticism; AURC, area under the ROC curve; BCS, body condition score; CI, confidence interval; CS, Cushing's syndrome; DM, diabetes mellitus; HAC, hyperadrenocorticism; MR, mineralocorticoid receptors; OR, odds ratio; PDH, pituitary dependent hyperadrenocorticism; ROC, receiver operating characteristic; SBP, systolic blood pressure; SH, systemic hypertension; TOD, target organ damage; UCCR, urinary cortisol to creatinine ratio; UD, urinary dipstick; UPC, urinary protein to creatinine ratio; USG, urinary specific gravity.

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1 | INTRODUCTION

Hyperadrenocorticism (HAC) is 1 of the most common endocrine diseases in middle-aged and old dogs characterized by a sustained cortisol overproduction by the adrenal cortex. Cortisol excess can result from an ACTH producing pituitary tumor (pituitary-dependent hyperadrenocorticism; PDH), secondary to an adrenal tumor (adrenal-dependent hyperadrenocorticism; ADH) or, less frequently, because of an ectopic ACTH secretion¹ or food dependent hypercortisolemia.² Chronic hypercortisolism might lead to several complications such as diabetes mellitus (DM), systemic hypertension (SH), proteinuria, glomerulosclerosis, pancreatitis, gallbladder mucocele, increased susceptibility to infections, or pulmonary thromboembolism among others, both in humans and dogs.³⁻²¹

Systemic hypertension associated with hypercortisolism is common in people, affecting 70%-85% of the patients.⁴⁻⁸ The pathophysiological mechanisms for hypertension in HAC are incompletely understood, but in people a multifactorial model has been proposed with many pathways involved: the renin-angiotensin system, an increased mineralocorticoid activity, the sympathetic nervous system, the vasoregulatory system, metabolic factors, vascular remodeling and sleep apnea.⁴⁻⁶ In human medicine, risk factors for hypertension associated with hypercortisolism are reported. In pediatric patients there is a positive correlation between SH and high circulating cortisol concentrations. In addition, SH is more frequent in pediatric patients with ACTH-independent Cushing's syndrome (CS).²² In adults, this tendency has also been observed in patients with ACTH-independent CS, but the prevalence of SH is similar for ACTH-dependent and independent hypercortisolism. Furthermore, in adults with CS, age, body mass index and duration of hypercortisolism have been associated with the development of SH, but no correlation is observed with circulating cortisol concentrations.⁷ Hypertensive human patients with hypercortisolism tend to have lower potassium blood concentrations than normotensive patients, especially those with ectopic CS in which hypokalemia is frequent and strongly associated with hypertension.^{7,23-25}

Systemic hypertension is also recognized in dogs with HAC with a prevalence between 31% and 86%.^{11-14,26-29} Some pathophysiological mechanisms have also been proposed, such as increased mineralocorticoid activity,^{30,31} decreased nitric oxide concentrations¹³ or increased renal vascular resistance.^{26,32} There are few studies assessing the risk factors for SH in dogs with HAC; in previous studies, no difference in the prevalence or severity of SH is observed between dogs with PDH or ADH and there is no correlation between systolic blood pressure (SBP) and age, sex, reproductive status or results of the ACTH-stimulation tests.¹¹ Previous studies have inconsistently identified a relationship between SBP and urinary protein to creatinine ratio (UPC) or baseline cortisol concentrations. A correlation between SBP and UPC but not with baseline cortisol concentrations has been described; however, other authors have found a correlation between SBP and baseline cortisol concentrations but not with UPC.¹¹⁻¹⁴

The objectives of our study were to determine the prevalence and severity of SH in dogs with naturally occurring HAC and to identify potential risks factors for SH in these dogs.

2 | MATERIALS AND METHODS

The clinical records of client-owned dogs with spontaneous HAC that presented to the Veterinary Teaching Hospital Complutense between January 2013 and December 2016 were retrospectively reviewed. On admission all owners signed a consent form authorizing the use of the data for research purposes.

Hyperadrenocorticism was suspected on the basis of compatible clinical signs (ie, polydipsia, polyuria, polyphagia, panting) and physical examination findings (ie, hair loss, thin skin, abdominal distension). The diagnosis of HAC was established when 2 of the following tests were positive: urinary cortisol to creatinine ratio (UCCR), ACTH-stimulation test or low dose dexamethasone suppression test (LDDST). Further work up included abdominal ultrasonography in all dogs. The results of the LDDST, high dose dexamethasone suppression test, endogenous ACTH plasma concentrations and ultrasound of the adrenal glands were used to differentiate between PDH and ADH.^{3,33-35} Exclusion criteria were dogs previously treated for HAC, dogs with chronic kidney disease (IRIS stage 3 or 4), dogs with cardiac disease (ACVIM consensus classification system stages C or D), or all three.^{36,37} Chronic kidney disease was staged based on serum creatinine, and SDMA when available, and subsequently substaged by proteinuria.³⁷ Thoracic radiographs and echocardiography were performed in dogs with a heart murmur, clinical signs compatible with cardiac disease, or both.³⁶

Signalment, clinical signs reported by the owner and duration of clinical signs before diagnosis, physical examination findings, presence of concurrent diseases and type of HAC were recorded. Body condition score (BCS) was also evaluated and dogs were classified as overweight (BCS \geq 7/9), ideal weight (BCS 4-6/9) or underweight (BCS \leq 3/9). Systolic blood pressure was measured in all dogs using Doppler ultrasonography method (Vetex Uni 900, Huntleigh Diagnostics Ltd., Cardiff, United Kingdom) with an 8 MHz flat probe placed between the carpal and the metacarpal pad of the left forelimb. Blood pressure was measured in sternal or lateral recumbency with minimal restraint. Cuff width was approximately 30%-40% of the extremity circumference at the site where cuff was placed.^{28,29} The final value of SBP was the mean value of 5 consecutive consistent measurements after, at least, 5 minutes' acclimation period and before performing any other procedure. If there was a consistent downward or upward trend in readings, further measurements were taken until consistent readings were achieved. Animals were classified as hypertensive when SBP was \geq 150 mm Hg and subclassified according to the risk of target organ damage (TOD) as mild hypertensive (150-159 mm Hg), moderate hypertensive (160-179 mm Hg) or severe hypertensive (\geq 180 mm Hg).^{28,29}

Clinicopathologic data (CBC, complete biochemistry profile and electrolytes, complete urinalysis and urinary culture, ACTH stimulation test, LDDS and UCCR) were also reviewed and included only when performed at our hospital to avoid differences in techniques and reference ranges. The biochemical profile included glucose, total plasma proteins, urea, creatinine, alanine-aminotransferase, alkaline-phosphatase, cholesterol, sodium, potassium, chloride and total calcium measurements. Serum and urinary cortisol concentrations were

measured by chemiluminescence immunoassay (Immulin 2000, Siemens Healthcare S.L.U, Madrid, Spain).

Urinalysis consisted in the measurement of urinary specific gravity (USG) by refractometry, performance of a urine dipstick (UD) and urinary sediment assessment. The USG was considered as low when values <1.030 were obtained. Urinary sediment was considered inactive when no bacteria were observed and less than 10 red blood cells, less than 5 white blood cells per high power field, or both were present. Urine for urinary culture was obtained by cystocentesis; samples were inoculated in blood agar plates and incubated at 37°C for 72 hours before considering them as negative. In cultures with bacterial growth, isolation of the microorganism and its subsequent identification were performed after standard procedures. Data of UPC were used in our study only when a negative culture and inactive sediment were present. For our study proteinuria was established as a $\text{UPC} > 0.5$.³⁷

Statistical analyses were performed using a computer software (IBM SPSS Statistics for Windows, v.25.0, IBM Corp., Armonk, NY). Normal distribution was assessed using Shapiro-Wilks test. As some of the variables studied did not follow a normal distribution when divided into groups, nonparametric tests were preferred. For categorical variables that were dichotomic, comparison among them were carried out using Fisher's exact test and for variables with more than 2 categories chi-square test was used (results expressed as percentage). When quantitative variables were compared between 2 groups, the Mann-Whitney sum rank test was performed and for those with 3 groups, Kruskal-Wallis test was used (results expressed as median, range, interquartile range [IQR]). Correlation between continuous variables was established using Spearman's rank correlation test. Risk was assessed for categorical variables calculating the odds ratio (OR) and 95% confidence interval (CI). For continuous variables receiver operating characteristic (ROC) curves were obtained to evaluate specificity and sensitivity of the different variables to predict SH; optimal cut-off point was obtained using Youden's index. A multivariate analysis was performed using logistic regression. Variables significantly associated in the univariate model were included in the multivariate analysis using Wald forward stepwise selection; variables with more than 30 missing data were not included in the multivariate analysis. In all cases, values of $P < .05$ were considered as statistically significant.

3 | RESULTS

Ninety clinical records were initially reviewed. Twenty-four dogs did not meet inclusion criteria; reasons for exclusion were chronic kidney disease IRIS stage 3 ($n = 2$), mitral valve disease stage C ($n = 1$) and previous trilostane treatment ($n = 21$). Therefore 66 dogs were finally included in the study.

3.1 | Signalment, type of HAC and concurrent diseases

Twenty-six dogs (39%) were males (14 neutered; 54%) and 40 (61%) were females (29 neutered; 73%). There were 26 cross breed dogs

and 40 purebred dogs. The following breeds were represented: Yorkshire Terrier ($n = 7$), miniature Schnauzer ($n = 4$), West Highland White Terrier ($n = 4$), English Cocker Spaniel ($n = 3$), miniature Poodle ($n = 3$), Boxer ($n = 2$), Scottish Terrier ($n = 2$), Pomeranian ($n = 2$), Pitbull Terrier ($n = 2$), Maltese ($n = 2$), Shih Tzu ($n = 2$), and 1 each of Bichon Frise, Border Collie, French Bulldog, English Bulldog, German Shepherd, American Cocker Spaniel, and Dachshund. Age ranged from 6 to 18 years old (median 11 years). Fifty-seven dogs had PDH (86%) and 9 ADH (14%); no dog was diagnosed with concurrent adrenal and pituitary HAC. Eight dogs (12%) had chronic kidney disease IRIS stage 2 and 7 dogs (11%) were diabetic. Four dogs (6%) were misdiagnosed with hypothyroidism and treated with levothyroxine for several months at their referring practice before diagnosis of HAC; in all of these dogs, levothyroxine supplementation was discontinued at least 15 days before SBP was measured. Additionally, 4 dogs (6%) had chronic pancreatitis; the diagnosis was based on clinical signs (eg, hyporexia, vomiting, diarrhea, or all three), increased canine pancreatic lipase immunoreactivity results and ultrasonographic findings. Median duration of clinical signs before diagnosis was 8 months (range 1-36 months).

3.2 | Clinical signs and physical examination findings

Polydipsia/polyuria was present in 60/66 dogs (91%) and polyphagia in 52/66 (79%). Hair loss was observed in 51/66 dogs (77%), skin abnormalities such as thin skin, hyperpigmentation or comedones were recorded in 49/66 dogs (74%) and 7/66 (11%) had lesions consistent with calcinosis cutis. Thirty-five dogs (53%) had abdominal distension and 41/66 (62%) panting reported by the owner. Neurological signs (seizures, circling, pressing, peripheral neuropathies, or all three) were present in 12/66 (18%) patients. Forty percent (25/66) of dogs were overweight and 4/66 (6%) were underweight.

3.3 | CBC, biochemistry, and urinalysis

Results of CBC, biochemistry, USG, UCCR, and UPC are shown in Table 1. The most frequent abnormalities found on CBC were thrombocytosis (25/66, 38%), lymphopenia (25/66, 38%) and eosinopenia (30/66, 45%). The most common findings in biochemistry were increased alanine-aminotransferase (40/66, 61%) and alkaline-phosphatase (55/64, 86%), hypercholesterolemia (24/41, 58%) and hyperglycemia (16/59, 27%). Urinalysis ($n = 62$) showed a low USG in 54 dogs (87%) and 15/62 dogs (24%) had an active sediment. Seven dogs (11%) had bacteriuria, 6/62 (10%) hematuria and 3/62 (5%) pyuria. Crystalluria was present in 9/62 animals (14%) with calcium oxalate in 2 of them (2/62, 3%). Urinary tract infection evaluated by urinary culture ($n = 50$) was present in 9 (18%) of the samples. Proteinuria evaluated by UD was observed in more than half of the dogs (34/62; 55%). A $\text{UPC} \geq 0.5$ was

present in 11/27 dogs (41%). Of the 19 dogs in which LDDST was performed, 10/19 (53%) showed lack of suppression (cortisol 4 hours and 8 hours >1 µg/dL and both >50% of basal cortisol), 4/19 (21%) partial suppression (cortisol 4 hours and 8 hours >1 µg/dL but at least 1 of them <50% of basal cortisol) and 5/19 (26%) showed an escape pattern (cortisol 4 hours <1 µg/dL and cortisol 8 hours >1 µg/dL).

3.4 | Systolic blood pressure

Systolic blood pressure ranged from 120 mm Hg to 280 mm Hg with a median value of 170 mm Hg (IQR 150-200 mm Hg). Hypertension was present in 54/66 dogs (82%). Six dogs were mildly hypertensive (9%), 18/66 moderately hypertensive (27%) and 30/66 severely hypertensive (46%).

3.5 | Comparisons between SBP and other variables

3.5.1 | Signalment, type of HAC, concurrent diseases, clinical signs and physical examination findings

Prevalence of SH was similar between dogs with ADH (8/9; 89%) and PDH (46/57; 81%) ($P = 1.0$). The median SBP of dogs with ADH (200 mm Hg, range 140-240 mm Hg, IQR 170-220 mm Hg) was higher than the median SBP of dogs with PDH (170 mm Hg; range 120-280 mm Hg, IQR 150-200 mm Hg) but the difference was not significant ($P = .09$).

The prevalence of SH among dogs with concurrent diseases was significantly lower for diabetic dogs (3/7; 43%) than for nondiabetic ones (51/59; 86%) with decreased odds of SH (OR = .118; 95%CI

TABLE 1 Descriptive statistics of the hematological, biochemical, and urinary variables studied

Parameter (units)	n	Median	Range		Reference Range		Number decreased (%)	Number increased (%)
			Min	Max	Min	Max		
Hematocrit (%)	66	48.7	21.8	63.2	37.0	55.0	5 (8%)	8 (12%)
Hemoglobin (g/dL)	66	16.6	7.1	21.7	12.0	18.0	5 (8%)	18 (27%)
RBC ($\times 10^6/\mu\text{L}$)	66	7.12	2.98	9.45	5.50	8.50	4 (6%)	3 (5%)
MCV (fL)	66	68.45	51.20	79.00	60.00	76.00	3 (5%)	4 (6%)
MCH (pg)	66	23.65	18.20	36.00	19.50	24.50	1 (1%)	15 (23%)
MCHC (g/dL)	66	34.00	13.50	39.30	32.00	36.00	2 (3%)	5 (8%)
Platelets ($\times 10^3/\mu\text{L}$)	66	438	186	962	200	500	1 (1%)	25 (38%)
WBC ($\times 10^3/\mu\text{L}$)	66	8.85	3.80	26.90	6.00	17.00	11 (17%)	1 (1%)
Mature neutrophils ($\times 10^3/\mu\text{L}$)	66	6.70	2.92	20.70	3.00	11.50	2 (3%)	4 (6%)
Immature neutrophils ($\times 10^3/\mu\text{L}$)	66	0.00	0.00	0.54	0.00	0.30	0 (0%)	3 (5%)
Lymphocytes ($\times 10^3/\mu\text{L}$)	66	1.18	0.32	4.90	1.00	4.80	25 (38%)	1 (1%)
Monocytes ($\times 10^3/\mu\text{L}$)	66	0.37	0.08	2.42	0.15	1.35	8 (12%)	5 (8%)
Eosinophils ($\times 10^3/\mu\text{L}$)	66	0.12	0.00	1.13	0.10	1.25	30 (45%)	0 (0%)
Basophils ($\times 10^3/\mu\text{L}$)	66	0.00	0.00	1.13	0.00	0.10	0 (0%)	0 (0%)
Glucose (mg/dL)	59	107	76	476	70	125	0 (0%)	16 (27%)
Urea (mg/dL)	65	32	20	168	10	58	0 (0%)	13 (20%)
Creatinine (mg/dL)	66	0.7	0.5	2.0	0.3	1.4	0 (0%)	8 (12%)
Cholesterol (mg/dL)	41	335	157	1135	125	310	0 (0%)	24 (58%)
Total plasmatic proteins (g/dL)	65	7.0	5.2	9.8	5.5	7.8	1 (1%)	11 (17%)
Alanine aminotransferase (U/L)	66	77	15	1764	10	60	0 (0%)	40 (61%)
Alkaline phosphatase (U/L)	64	547	26	7452	25	110	0 (0%)	55 (86%)
Sodium (mEq/L)	28	148	141	161	140	155	0 (0%)	1 (4%)
Potassium (mEq/L)	53	4.2	3.1	5.4	3.8	5.8	10 (19%)	0 (0%)
Chloride (mEq/L)	24	110	102	128	105	125	3 (13%)	1 (4%)
Total calcium (mg/dL)	41	9.7	7.30	11.90	8	13	1 (2%)	0 (0%)

Note: In the table number of animals (n), median value, range (Min, minimum; Max, maximum), reference range and number of animals outside the reference range are described.

Abbreviations: RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentrations; WBC, white blood cells.

.022-.626; $P = .02$). Median SBP was also significantly lower ($P = .03$) in dogs with DM (140 mm Hg, range 120-200 mm Hg, IQR 125-170 mm Hg) compared to nondiabetic dogs (170 mm Hg, range 120-280 mm Hg, IQR 160-200 mm Hg), however no correlation was observed with severity of hypertension. Dogs previously misdiagnosed with hypothyroidism and treated with levothyroxine did not have a higher prevalence of SH (3/4, 75%) compared to the rest of the population (51/62, 82%; $P = .56$). Furthermore, dogs with chronic kidney disease IRIS stage 2 did not have higher prevalence of SH (7/8, 88%) compared to those without renal disease (47/58, 81%; $P = 1.0$).

No correlation was observed between the prevalence of SH nor the median SBP values with age, breed, sex or reproductive status. Clinical signs, duration of clinical signs or physical examination findings were not correlated with SH nor SBP.

3.5.2 | CBC and biochemistry

Hypertensive dogs had significantly higher median platelet count ($487.50 \times 10^3/\mu\text{L}$, range 186.00 - $962.00 \times 10^3/\mu\text{L}$, IQR 368.00 - $570.00 \times 10^3/\mu\text{L}$) than normotensive ones ($293.00 \times 10^3/\mu\text{L}$, range 242.00 - $436.00 \times 10^3/\mu\text{L}$, IQR 272.50 - $382.00 \times 10^3/\mu\text{L}$) ($P = .001$). Area under the ROC curve (AURC) was .802 (95%CI = .698-.907; $P = .001$) showing that platelet values $\geq 438 \times 10^3/\mu\text{L}$ had a specificity of 100% and a sensitivity of 61.1% to predict SH (Figure 1). Prevalence of SH was also significantly higher in patients with thrombocytosis (platelet count $\geq 500 \times 10^3/\mu\text{L}$) (100%, 25/25) compared to dogs with a normal platelet count (54%; 29/41; $P = .002$). No correlation was observed with the remaining parameters of the CBC.

Among biochemical parameters evaluated, only potassium ($n = 53$) and Na/K ratio ($n = 28$) were significantly correlated with SBP. Serum potassium concentrations shown a significant negative correlation with SBP ($r = -0.315$, $P = .02$); median potassium concentrations were significantly lower in hypertensive dogs (4.1 mEq/L, range 3.1-5.4 mEq/L, IQR 3.9-4.3 mEq/L) than in normotensive ones (4.5 mEq/L, range 4.0-5.0 mEq/L, IQR 4.3-4.7 mEq/L) ($P = .007$) and were also significantly lower in severely hypertensive dogs (4.1 mEq/L, range 3.1-5.1 mEq/L, IQR 3.9-4.2 mEq/L) compared to the rest of the population (4.3 mEq/L, range 3.3-5.4 mEq/L, IQR 3.9-4.6 mEq/L; $P = .03$). The AURC for serum potassium was 0.789 (95%CI = 0.655-0.953; $P = .007$) and values ≤ 4.35 mEq/L had a specificity of 88.9% and sensitivity of 65.9% to detect SH (Figure 2). All dogs with hypokalemia (potassium concentration < 3.8 mEq/L) (10/53 dogs, 19%) were hypertensive, however there was not a significant difference in SH prevalence when compared with those dogs with potassium concentrations within the reference range (34/43, 79%; $P = .18$).

Na/K ratio was positively correlated with SBP ($r = 0.497$, $P = .007$), was significantly higher in hypertensive dogs (35.85, range 29.02-46.36) than in normotensive dogs (32.44, range 31.15-33.72, IQR 32.20-33.33; $P = .05$) and was also significantly higher in severely hypertensive dogs (36.15, range 29.02-42.06, IQR 34.93-38.59) compared to the rest of the dogs (32.44, range 30.00-46.36, IQR 32.17-34.65; $P = .02$). The AURC was similar than the 1 obtained for serum

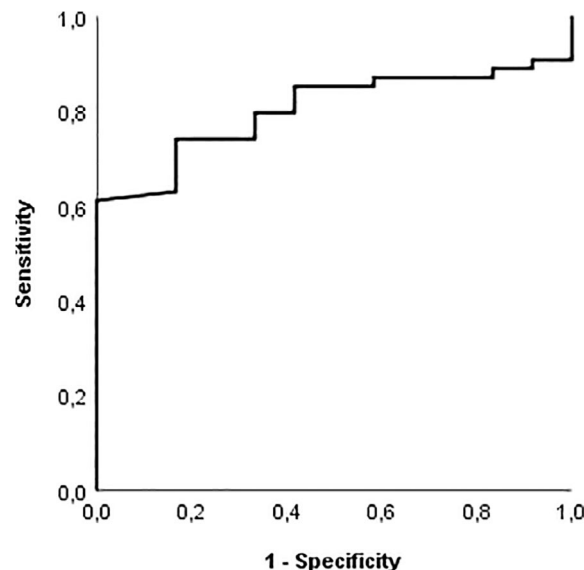


FIGURE 1 Receiver operating characteristic (ROC) curve assessing platelet count as a predictor of systemic hypertension. Area under the ROC curve was 0.802 (95%CI = 0.698-0.907)

potassium concentrations (0.787, 95%CI = 0.625-0.949; $P = .05$) and values of Na/K ≥ 33.8 had a specificity of 100% and a sensitivity of 73.9% to predict SH.

3.5.3 | Urinalysis, UPC, and urinary culture

Median USG ($n = 62$) was significantly lower in hypertensive dogs (1.012, range 1.001-1.058, IQR 1.007-1.017) than in normotensive ones (1.025, range 1.009-1.043, IQR 1.015-1.035) ($P = .006$). Dogs with a low USG (≤ 1.029) had significantly higher prevalence of SH (48/54; 89%) than those with a USG ≥ 1.030 (4/8, 50%; $P = .02$). Of the 8 dogs with USG ≥ 1.030 , 3/8 (38%) were diabetic ($P = .02$). As DM was found to be associated with lower SBP, dogs with DM were eliminated and USG analysis was reconsidered. In nondiabetic dogs, no differences were observed in the median USG between hypertensive (1.012, range 1.001-1.058, IQR 1.007-1.017) and normotensive dogs (1.018, range 1.009-1.043, IQR 1.013-1.029; $P = .12$), nor in the prevalence of SH between dogs with a USG below 1.030 (46/51, 90%) or ≥ 1.030 (4/5, 80%; $P = .44$). All dogs with chronic kidney disease had a USG below 1.030 (8/8, 100%), but no significant difference in the number of animals with an USG below this value was observed when compared with the rest of the population (46/54, 85%; $P = .58$). Median USG values were also not significantly different between dogs with CKD and those without it.

When proteinuria was assessed by UD ($n = 62$), proteinuric dogs had significantly higher median SBP values (182 mm Hg, range 130-280 mm Hg, IQR 160-210 mm Hg) and higher prevalence of SH (32/34, 94%) than those without proteinuria (160 mm Hg, range 120-240 mm Hg, IQR 143-180 mm Hg [$P = .005$], and 20/28, 71% [$P = .03$], respectively). Prevalence of severe SH was also significantly

higher in dogs with proteinuria evaluated by UD (20/34, 59%) compared to nonproteinuric dogs (8/28, 29%; $P = .02$).

Dogs with a UPC ≥ 0.5 had significantly higher median SBP (210 mm Hg, range 120–280 mm Hg, IQR 165–235 mm Hg) than that of nonproteinuric (160 mm Hg, range 120–230 mm Hg, IQR 148–192 mm Hg; $P = .03$) although prevalence of SH was similar for both groups and proteinuria did not increase the odds for SH. The AURC for UPC was poor (0.644, 95%CI = 0.469–0.858) and thus, cut-off points are not provided.

No differences were observed in USG and proteinuria (evaluated by UD or UPC) between dogs with chronic kidney disease and those without. Data from urinary sediment and urinary culture were not correlated with SBP, however all dogs with hematuria were hypertensive.

3.5.4 | Plasma and urinary cortisol concentrations

Plasma and urinary cortisol concentrations were not significantly correlated with SBP and did not differ between hypertensive and

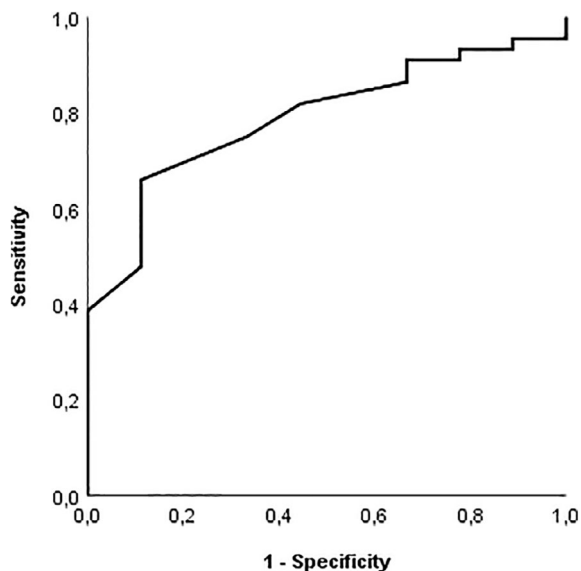


FIGURE 2 Receiver operating characteristic (ROC) curve assessing potassium concentrations as a predictor of systemic hypertension. Area under the ROC curve was 0.789 (95% CI = 0.655–0.953)

nonhypertensive dogs (Table 2). Only 1/19 (5%) dogs in which LDDST was performed was normotensive; thus median cortisol concentrations between normotensive and hypertensive animals were not compared and prevalence of SH between the different patterns of the LDDST is not provided. Median SBP values were lower in dogs with a LDDST partial suppression pattern (157 mm Hg, range 146–180 mm Hg, IQR 150–170 mm Hg) than in dogs with lack of suppression (192 mm Hg, range 160–220 mm Hg, IQR 165–210 mm Hg) or an escape pattern (185 mm Hg, range 170–280 mm Hg, IQR 170–200 mm Hg), but the difference was not significant ($P = .07$). Also, Na/K ratio was positively correlated with the post ACTH cortisol concentrations ($r = 0.458$; $P = .05$) and UCCR ($r = 0.489$; $P = .03$).

3.5.5 | Multivariate risk analyses

In a multivariate analysis the final model included 3 variables: platelet count (OR = 1.011, 95%CI = 1.002–1.020; $P = .02$), potassium concentrations (OR = 0.066, 95%CI = 0.007–0.627; $P = .02$) and presence of DM (OR = 0.060, 95%CI = 0.005–0.765; $P = .03$).

4 | DISCUSSION

Systemic hypertension was present in 82% of dogs with naturally occurring HAC and nearly half of the dogs had severe hypertension (SBP ≥ 180 mm Hg) with increased risk of TOD. Systemic hypertension was associated with thrombocytosis, lower serum potassium concentrations and proteinuria. Diabetes mellitus seemed to be a protective factor for SH in dogs with HAC.

Systemic hypertension is highly prevalent in both humans and dogs with hypercortisolism.^{3–7,11–14,26–29} However, few studies have focused on the prevalence and risks factors for SH in dogs with naturally occurring HAC. In our study, the prevalence of SH was high (82%) and similar to data (70–85%) from people with CS.^{4–7} Prevalence of SH in the present study was similar to that reported in dogs with HAC in a previous study,¹¹ although slightly higher than described by others.^{12–14,16,26,32} The fact that prevalence of SH in the present study was close to the upper reported range, might have been because of the cut-off value used to define SH. In the present study, SH was considered as a SBP ≥ 150 mm Hg (consistent with the ACVIM

TABLE 2 Plasma and urinary cortisol concentrations ($\mu\text{g/dL}$) between hypertensive (systolic blood pressure ≥ 150 mm Hg) and normotensive (systolic blood pressure < 150 mm Hg) dogs with hyperadrenocorticism

Variable	Category	Median	Minimum	Maximum	IQR (Q1–Q3)	P value
Basal cortisol concentrations ($\mu\text{g/dL}$)	Normotensive	4.27	2.92	8.06	3.08–6.67	.90
	Hypertensive	4.43	0.75	15.30	3.40–6.15	
Cortisol concentrations 1-hour post ACTH ($\mu\text{g/dL}$)	Normotensive	19.85	16.90	24.20	17.90–22.50	.68
	Hypertensive	21.50	11.60	91.00	16.50–30.45	
Urinary cortisol to creatinine ratio	Normotensive	121.5	106	186	113.5–152.5	1.0
	Hypertensive	179	51	1769	101.5–286.5	

consensus statement²⁸) while, in the majority of the previous studies, SH is defined as a SBP ≥ 160 mm Hg.^{13,14,26} Also, the higher prevalence might be partially influenced by the fact that approximately 30% of the patients included in the study were referral cases. In any case, comparisons between studies are challenging because of the differences in inclusion criteria, the variability in the definition of SH and different blood pressure measurement techniques. In our study we included all dogs with HAC (ADH and PDH). Nevertheless, the prevalence or severity of SH between dogs with PDH and ADH was not significantly different. Classification of hypertension was based on the risk for TOD following the ACVIM consensus for SH in dogs,²⁸ and the prevalence of severe hypertension (≥ 180 mm Hg) in our study was higher than previously reported¹¹; this might be partially explained by the definition of severe hypertension used by these authors (SBP ≥ 190 mm Hg). Given the high prevalence of SH in both studies, and especially severe SH (regardless which cut-off value is used, the risk for TOD for a dog with a SBP ≥ 180 mm Hg is high), SBP should be assessed in dogs whenever a diagnosis of HAC is suspected.

The population characteristics (age, sex, reproductive status and breed) of the dogs included in our study, as well as the proportion of dogs with PDH or ADH, were in agreement with the literature.^{3,38-40}

Age, BCS, sex and reproductive status were not related to SBP as found in a previous study.¹¹ Age has been related to SH in adults with CS,⁷ however, an increase in SBP related to age is well recognized in the general human population,⁴¹ so it is unclear whether age is an independent factor for the development of SH for people with hypercortisolism. In dogs, the effect of age on systemic blood pressure is uncertain. A small increase in SBP of 1-3 mm Hg per year has been noted with aging in some studies but such finding has not been observed by others.^{29,42-44} Also, and contrary to our findings, in humans with hypercortisolism, a relationship between body mass index and hypertension has been observed. In humans with CS, the prevalence of obesity (57%-100%) is higher than observed in the dogs of our study (40%), and it is usually related with the presence of metabolic syndrome, central adiposity and sleep apnoea, that can contribute to hypertension.^{4-7,45} In dogs, the presence of metabolic syndrome has not been demonstrated.⁴⁶ Also, in obese dogs SH is an uncommon finding and obesity has not been described as risk factor for SH.^{29,42,43,47}

In adults with CS, duration of hypercortisolism has been related with SH⁷; however, in pediatric patients, in which duration of clinical signs before diagnoses is approximately 6 months, the prevalence of SH is also high (50%-90%).^{22,48} In the present study, SH in dogs was not correlated with duration of clinical signs which might suggest similarities with the development of SH in pediatric patients with CS.

Origin of HAC (PDH or ADH) was not associated with SBP or with the prevalence of SH as previously reported.¹¹ This reflects that SH associated with HAC is related to the effects of chronic hypercortisolism rather than the consequences derived from an adrenal mass or hypertension secondary to neoplasia. However, a tendency was observed for a higher SBP in dogs with ADH similar than observed in people with CS.⁸ Studies including a larger number of

dogs with ADH are needed because the small number of dogs with an adrenal mass could have led to type II errors. Similar to observed in people with CS and also in dogs with HAC,^{5,7,11} a correlation between plasma or urinary cortisol concentrations and SBP was not observed. This lack of correlation with the degree of hypercortisolism suggests that, hypertension in dogs with HAC, has probably a multifactorial etiology, similar to proposed in human medicine, and not only dependent of cortisol concentrations.⁴⁻⁷

Concurrent diseases known to affect SBP were not a risk factor for SH. In the present study, 11% of dogs had overt DM at diagnosis, which is in agreement with the data from the veterinary literature,⁴⁹ but lower than from human medicine (32%-45%),^{7,8,10} suggesting that DM associated with hypercortisolism is less frequent in dogs than in humans. It is unknown why some dogs with HAC develop DM while others do not. It is hypothesized that hypercortisolism in dogs could act as a trigger in those animals with a pre-existing pancreatic lesion.⁵⁰ In human medicine, hypercortisolism is linked with central obesity and metabolic syndrome, which also contributes to peripheral insulin resistance and finally can lead to type II DM.¹⁰ However, metabolic syndrome has not been demonstrated in dogs,⁴⁶ and despite obesity induces insulin resistance in dogs, there is no evidence that obese dogs develop type II DM.^{46,50,51} This might explain the lower prevalence of DM in dogs with HAC compared to humans with CS. In our study, the prevalence of SH in dogs with DM and HAC was 42.9%. These results are slightly lower than described by other authors for dogs with DM (55%-67%),^{52,53} but similar to those reported in other studies for dogs with DM (46%)⁵⁴ and also for dogs with both conditions (50%).²⁶ Interestingly, in our study, dogs with concurrent DM and HAC had lower prevalence of SH than those with isolated HAC, and lower SBP values. In people with CS, metabolic syndrome, visceral obesity, and insulin resistance, are thought to contribute to SH, as they promote sleep apnea, atherosclerosis and vascular remodeling.⁴⁻⁶ However, a study evaluating cardiovascular risks in patients with CS could not find significant differences in SBP between patients with DM, impaired glucose metabolism, or those with normal glucose metabolism.⁷ Nevertheless, this do not explain the lower risk for SH found in our study for diabetic dogs. Our results suggest that in dogs with HAC, DM was not a risk factor for the development of SH. However, as only 7 diabetic dogs were included in the present study, these results should be interpreted with caution. Further research including a larger number of dogs with both conditions is needed to elucidate this finding.

Thrombocytosis was a common finding in this population of dogs, which has also been previously described in dogs and people with hypercortisolism.^{3,9,33,55,56} Even though the mechanisms promoting thrombocytosis in dogs with HAC are incompletely understood, they are thought to be the result from direct bone marrow stimulation.^{3,55,57} In our study all dogs with a platelet count above $438 \times 10^3/\mu\text{L}$, and in consequence all dogs with thrombocytosis, were hypertensive; to our knowledge this finding has not been previously reported. In people with cortisol-induced hypertension, an increase in erythropoietin concentrations has been observed.⁵⁸ In people and dogs, erythropoietin has a direct effect on megakaryocytes,^{59,60} has a

direct vasoconstrictor effect and has been proposed as a possible mechanism for the development of SH in humans with CS.⁵⁸ Also in people with CS, an increased oxidative stress leading to platelet activation via thromboxane-A2 (TXA2) has been observed.^{61,62} TXA2 is a potent vasoconstrictor that also contributes to platelet release, activation and aggregation.^{5,6,9,63} Both erythropoietin and TXA2 might play a role in glucocorticoid-induced hypertension in dogs but further studies are needed to support this theory.

Biochemical abnormalities were similar than previously reported.^{3,33,40} Potassium concentrations and Na/K ratio were significantly correlated with SBP. A difference in the potassium concentrations between dogs with and without SH and between dogs with severe hypertension was also observed; moreover, all hypokalemic patients ($K < 3.8$ mEq/L) were hypertensive. These findings might suggest that mineralocorticoid receptors (MR) could be involved in the development of SH in dogs with HAC. The MR has the same affinity to aldosterone and cortisol, but not to cortisone.⁶⁴⁻⁶⁶ The enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) converts cortisol in to cortisone, and it is abundantly expressed in the classical mineralocorticoid target tissues (eg, renal cortex, vascular endothelium and smooth muscle cells), binding the selectivity of MR to aldosterone.^{64,67-69} Hypercortisolism saturates the 11 β -HSD allowing cortisol to bind the MR and resulting in a cortisol induced apparent mineralocorticoid excess. In people with hypercortisolemia, this feature has been associated with sodium retention and potassium excretion, which could contribute to the development of SH.^{5-7,23,25,45,66-68,70-72}

Previous studies in dogs with PDH have found decreased aldosterone concentrations when compared with healthy controls.^{30,31} This has been proposed to be the result of an apparent mineralocorticoid excess caused by glucocorticoid-induced MR saturation,³⁰ but also to be secondary to the transformation of zona glomerulosa cells into zona fasciculata-like cells.³¹ It is possible, as in humans with CS, that the reduced aldosterone concentrations in dogs with HAC occurs, at least partially, from saturation of MR, leading to lower serum potassium concentrations, higher renal sodium reabsorption and SH. Saturation of MR might explain the relationship found in our study between SH and potassium concentrations. However, further studies evaluating aldosterone, 11 β -HSD activity, urinary electrolytes, and its relation with SH are needed.

A correlation between a low USG and hypertension was observed in our study; however, in the nondiabetic dogs, no correlation was shown between USG and SH. This might suggest that the high proportion of diabetic animals in the group of dogs with a USG ≥ 1.030 was reducing its prevalence of SH rather than the existence of a direct relationship between USG and SH.

Proteinuria (defined as UPC ≥ 0.5) was common, being present in 40.7% of dogs, similar to previous reports.^{11,13,17} Prevalence of SH was similar between proteinuric and nonproteinuric dogs although median SBP values were higher in proteinuric dogs, in agreement with others.¹¹ Relationship between SBP and proteinuria in dogs with HAC has been inconsistent in previous studies.^{11-14,32} Glucocorticoid-induced hypertension in dogs can lead to an increase in renal plasma flow, boosting the intraglomerular pressure, potentially contributing

to proteinuria.^{13,73-75} Other authors, however, have not found a correlation between proteinuria and SH in dogs with HAC, suggesting that the development of proteinuria in these dogs is multifactorial, and other mechanisms such as dyslipidemia, impaired endothelial function, glomerulosclerosis and a hypercoagulability status might also play a role.^{11,12,14,32}

The design of the study is subject to some limitations, mainly derived from its retrospective nature. Even though SBP measurement is a standardized procedure at our institution, because the lack of prospective assessment the technique was subjected to individual variations and documentation of stressful events was not available. Also not all the variables were available for all the patients and other risk factors not assessed might be present. Unfortunately, because of the retrospective nature of the study, aldosterone was not measured, making it difficult to provide conclusions about the relationship between potassium and SH and the possible role of MR in the development of SH in dogs with HAC.

Another potential limitation is that no device for blood pressure measurement has been completely validated in conscious dogs at the time of writing.²⁹ Doppler is the technique used at our institution and the protocol follows the ACVIM guidelines recommendations trying to maximize the chances of obtaining reliable results.^{28,29} Studies performed in awake conscious dogs with Doppler ultrasonography and oscillometry compared to invasive arterial blood pressure, have shown that none of these devices satisfy all the ACVIM criteria for validation.^{29,76-78} High definition oscillometry allows evaluation the arterial wave for artifacts, which might lead to obtaining more reliable measurements compared to other devices.⁷⁹ However, in a study comparing high definition oscillometry and Doppler ultrasonography in awake dogs, the results showed that SBP values were similar for both devices.⁸⁰

In conclusion, SH, which is frequently severe, is common in dogs with HAC and blood pressure should be routinely assessed in dogs with a suspicion of HAC. In those cases in which blood pressure cannot be routinely evaluated, the presence of thrombocytosis, low potassium concentrations and proteinuria should raise concerns about possible SH and the risk of TOD and might incite the clinician to perform this procedure. The association between SH and potassium concentrations might suggest a role of MR in the development of hypertension in these dogs; however further studies are needed to investigate the relationship between SH, aldosterone and 11 β -HSD activity in dogs with HAC. Finally, dogs with concurrent DM and HAC seemed to have a reduced risk of development of SH; this finding should be further investigated.

ACKNOWLEDGMENTS

Royal Canin kindly contributes to research in veterinary endocrinology at the Veterinary Teaching Hospital Complutense.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

This study has been approved by the hospital board of the Veterinary Teaching Hospital Complutense. All owners signed a consent at admission at the center allowing to use the data from their pets for research purposes.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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How to cite this article: García San José P, Arenas Bermejo C, Clares Moral I, Cuesta Alvaro P, Pérez Alenza MD. Prevalence and risk factors associated with systemic hypertension in dogs with spontaneous hyperadrenocorticism. *J Vet Intern Med*. 2020;1-11. <https://doi.org/10.1111/jvim.15841>