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Use of Computed Tomography Adrenal Gland Measurement for Differentiating ACTH Dependence from ACTH Independence in 64 Dogs with Hyperadenocorticism

M.I. Rodríguez Piñeiro, P. de Fornel-Thibaud, G. Benchekroun, F. Garnier, C. Maurey-Guenec, F. Delisle, and D. Rosenberg

Background: The measurement of adrenal gland size on computed tomography (CT) scan has been proposed for the etiological diagnosis of hyperadrenocorticism (HAC) in dogs. Symmetric adrenal glands are considered to provide evidence for ACTH-dependent hyperadrenocorticism (ADHAC), whereas asymmetry suggests ACTH-independent hyperadrenocorticism (AIHAC). However, there are currently no validated criteria for such differentiation.

Objective: The aim of this retrospective study was to compare various adrenal CT scan measurements and the derived ratios in ADHAC and AIHAC cases, and to validate criteria for distinguishing between these conditions in a large cohort of dogs.

Animals: Sixty-four dogs with HAC (46 ADHAC, 18 AIHAC).

Methods: Dogs with confirmed HAC and unequivocal characterization of its origin were included. Linear measurements of adrenal glands were made on both cross-sectional and reformatted images.

Results: An overlap was systematically observed between the AIHAC and ADHAC groups for all measurements tested. Overlaps also were observed for ratios tested. For the maximum adrenal diameter ratio derived from reformatted images (rADR), only 1/18 AIHAC dogs had a rADR within the range for ADHAC. For a threshold of 2.08, the 95% confidence intervals for estimated sensitivity and specificity extended from 0.815 to 1.000 and from 0.885 to 0.999, respectively, for AIHAC diagnosis.

Conclusion and Clinical Importance: Measurements from cross-sectional or reformatted CT scans are of little use for determining the origin of HAC. However, rADR appears to distinguish accurately between ADHAC and AIHAC, with a rADR > 2.08 highly suggestive of AIHAC.

Key words: Adrenal gland; Computed tomography; Diagnostic imaging; Endocrinology; Hyperadrenocorticism.

Hyperadrenocorticism (HAC), or Cushing's syndrome, is a commonly diagnosed endocrine disorder in dogs. Adrenocorticotropic hormone (ACTH)-dependent hyperadrenocorticism (ADHAC) is the most common form of HAC. The presence of a pituitary adenoma usually is responsible for this condition, although rare examples of ectopic secretion have occasionally been described.[1–3] HAC is ACTH-independent hyperadrenocorticism (AIHAC) in 10–15% of affected dogs. The major form of AIHAC is triggered by a functional adrenocortical tumor, adenoma, or carcinoma, and is known as adrenal-dependent hyperadrenocorticism (ADH). One case of food-dependent AIHAC also has been described recently.[2,4]

Correct differentiation between ADHAC and AIHAC is essential for prognosis and treatment decisions. Over the last 30 years, imaging techniques and endocrine tests have been developed for this purpose.[5–13] Pituitary enlargement can be identified in pituitary-dependent HAC, the main form of ADHAC, on computed tomography (CT) scans, for example,[14,15] but pituitary-dependent HAC with a pituitary gland of normal appearance also may occur,[2,16,17] presumably resulting from an overlap

Abbreviations:

ACTH	adrenocorticotropic hormone
ADHAC	ACTH-dependent hyperadrenocorticism
AIHAC	ACTH-independent hyperadrenocorticism
Ao	aorta diameter
CT	computed tomography
DST	dexamethasone suppression test
HAC	hyperadrenocorticism
HDDST	high-dose dexamethasone suppression test
LAD	maximum diameter of the larger adrenal gland
LDDST	low-dose dexamethasone suppression test
rADR	adrenal diameter ratio on reformatted images
rALR	adrenal length ratio on reformatted images
rLAD	maximum diameter of the larger adrenal gland on reformatted images
rLAL	maximum length of the larger adrenal gland on reformatted images
rSAD	maximum diameter of the smaller adrenal gland on reformatted images
rSAL	maximum length of the smaller adrenal gland on reformatted images
SAD	maximum diameter of the smaller adrenal gland
SAL	maximum length of the smaller adrenal gland
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From the Internal Medicine Unit, National Veterinary School of Alfort, Maisons-Alfort, France (Rodríguez Piñeiro, Benchekroun, de Fornel-Thibaud, Maurey-Guenec, Delisle, Rosenberg); the Internal Medicine Unit, National Veterinary School of Lyon, Marcy l'Étoile, France (Rodríguez Piñeiro); the Veterinary Anticancer Center, Maisons-Alfort, France (de Fornel-Thibaud, Delisle); and the Biochemistry Unit, National Veterinary School of Lyon, Marcy l'Étoile, France (Garnier). Part of this work was presented at the ECVIM-CA Congress, in Porto (Portugal), in September 2009.

Corresponding author: D. Rosenberg, DVM, PhD, Internal Medicine Unit, National Veterinary School of Alfort, 7 avenue du Général de Gaulle, 94704 Maisons-Alfort, France; e-mail: drosenberg@vet-alfort.fr

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with the appearance of the pituitary gland in dogs with AIHAC. Measurement of the adrenal glands by imaging is an obvious strategy for determining the cause of HAC. Symmetric normal sized or enlarged adrenal glands are expected in ADHAC, whereas strong asymmetry is expected in cases of AIHAC caused by unilateral functional adrenal tumors.[18,19] CT measurements of the adrenal glands occasionally have been reported in healthy dogs, dogs with adrenal tumors and dogs with adrenal hyperplasia because of ADHAC, and different methods have been described for determining maximum diameter and length,[14,20–22] as well as the volume of the adrenal glands.[23,24] Cross-sectional views initially were considered for the measurement of maximum adrenal gland diameter.[14] However, there is a risk of miscalculation with this technique when the long axis of the measured adrenal gland is not perpendicular to the transverse view. Obtaining transverse views from reformatted images is feasible with new software.[23] This strategy could optimize the fit to the short axis of the adrenal glands. Adrenal gland length also can be calculated from reformatted images, but the use of this method in dogs has not been reported. The accuracy, for discrimination between ADHAC and AIHAC, of maximum adrenal gland diameter on transverse or reformatted CT scans and of adrenal gland length on reformatted images or of any other ratio calculated from CT scan measurements, has not been determined in a large cohort of dogs.

The aims of this study were to evaluate the accuracy of adrenal length and diameter measurements taken on CT scans for the etiologic diagnosis of HAC in a large cohort of dogs, and to compare the performance of maximum diameter measurements and derived ratios obtained from cross-sectional and reformatted images for distinguishing between AIHAC and ADHAC.

Materials and Methods

Clinical Cases

The medical records of dogs evaluated at the Internal Medicine Unit of the National Veterinary School of Alfort (France), between January 1, 2003 and April 30, 2010, were reviewed. Included were all dogs with:

(1) A history, physical examination, biochemical, and hematological findings consistent with HAC.
(2) At least 1 endocrine test result, ACTH stimulation test, or low-dose dexamethasone suppression test (LDDST) supporting the diagnosis of HAC.
(3) Unequivocal determination of the origin of HAC. For dogs in this study, this determination was based on the measurement of ACTH concentration. Because the inclusion period of this study overlapped that of a previous study evaluating the accuracy of ACTH determination for etiologic diagnosis in HAC, dogs included in both studies were assigned to the ADHAC group only if a dexamethasone suppression test (DST) was performed and feedback inhibition was observed, and to the AIHAC group in cases of histologic analysis showing the presence of a functional adrenal tumor. For dogs included in this study, additional information for HAC characterization (feedback inhibition in response to DST and histologic features of adrenocortical tissue removed by surgery or necropsy) was collected when available.
(4) Pituitary and abdominal CT scans were performed before treatment.

Endocrine Tests and Hormone Assays

Plasma cortisol concentrations were determined by dynamic endocrine tests, with a kit[a] validated previously in dogs.[25] The ACTH stimulation test, based on the IV administration of 0.25 mg of tetracosactide,[b] the LDDST, based on the IV administration of dexamethasone[c] at a dosage of 0.01 mg/kg of body weight, and the high-dose dexamethasone suppression test (HDDST), based on the IV administration of 0.1 mg/kg body weight of dexamethasone, were performed as described previously.[6,11,26–28] Hyperadrenocorticism was confirmed by a marked increase in serum cortisol concentration ($\geq$500 nmol/L) 1 hour after ACTH stimulation, an inadequate decrease in serum cortisol concentration ($\geq$40 nmol/L) 8 hours after dexamethasone injection, or both. ADHAC was demonstrated by feedback inhibition 4 or 8 hours after dexamethasone injection in the DST. For the LDDST, feedback inhibition was defined as a 4-hour cortisol concentration $<$40 nmol/L or $<$50% of the basal concentration, or an 8-hour cortisol concentration $<$50% of the basal concentration but $\geq$40 nmol/L. For the HDDST, feedback inhibition was defined as a 4-hour or 8-hour serum cortisol concentration $<$40 nmol/L or $<$50% of the basal concentration.[11]

Blood samples for ACTH determination were collected from the jugular vein into EDTA-coated tubes. The samples were immediately centrifuged at 4°C, 500 × *g* for 8 minutes, and the resulting plasma was transferred to plastic tubes and stored at −80°C until required. Plasma ACTH concentrations were determined with Immulite ACTH,[d] validated previously for dogs, run on an Immulite 2000 analyzer.[d,29] All dogs with an unsuppressed ACTH concentration ($\geq$6 pg/mL) were considered to have ADHAC, and dogs with an ACTH concentration below the limit of quantification of the assay ($<$5 pg/mL) were considered to have AIHAC.[13]

CT Scans

Food was withheld from the dogs for 12 hours before CT examination of the pituitary and adrenal glands. Anesthesia was induced by the IV administration of 6.5 mg/kg of propofol (1 g/100 mL)[e] and was maintained with inhaled isoflurane[f] and oxygen. With dogs in sternal recumbency, a CT scan of the neurocranium, between the external occipital protuberance and the cribiform plate, before and 1–2 minutes after the IV injection of contrast medium[g] (2 mL/kg), administered as a hand-injected bolus, was performed with a helical CT scanner.[h] The scanning parameters were as follows: full axial modality, 120 kVp, 90–224 mA, 512–512 matrix, 3-mm-thick consecutive slices. A contrast-enhanced CT scan of the cranial abdomen was obtained 5–10 minutes after postcontrast image acquisition for the pituitary gland region. The scanning parameters were as follows: helical modality, 0.7 s/rotation, standard algorithm, 120 kVp, 100–130 mA, 512–512 matrix, 1.25 mm slice thickness, pitch 0.625 : 1.

All images were transferred to a workstation[i] and analyzed by one of the authors blinded to the origin of HAC for each dog.

Pituitary images were evaluated with the same window settings (window width 250, window length 80). Homogeneous or heterogeneous contrast enhancement of the pituitary gland was noted and the pituitary height/brain area (P/B) ratio was calculated as the ratio of pituitary gland height (mm) to brain area (mm^2).[16,28] Pituitary glands with a P/B ratio $\leq 0.31\times10^{-2}\,mm^{-1}$ were considered normal in size, and those with a P/B ratio $> 0.31\times10^{-2}\,mm^{-1}$ were considered enlarged, as described previously.[16]

Abdominal images were evaluated with standard abdominal windowing (400 window width/40 window level). Cross-sectional and reformatted images were examined.

On cross-sectional images, the adrenal glands were round to oval. For apparently oval glands, the largest diameter of the section was measured and, after evaluation of all sections of each gland, only the maximum diameters of the larger (LAD) and smaller (SAD) adrenal glands were recorded. The impact of the choice of cross-sectional view chosen on aorta diameter (Ao) calculation was investigated in 5 dogs selected randomly. On day 1, Ao was measured on the cross-sectional view on which the LAD was obtained. On day 2, Ao was measured on the cross-sectional view on which the SAD was obtained. On day 3, all cross-sectional views containing at least 1 adrenal gland subsequently were numbered cranio-caudally and Ao was measured on the median view. There was systematically $<5\%$ difference among the means of these 3 measurements and these differences therefore were considered nonsignificant. By way of consequences, Ao was measured as on day 3 for all dogs. The following ratios were calculated: LAD/Ao, SAD/Ao, and the adrenal diameter ratio (ADR), defined as the ratio of the maximum diameters of the 2 adrenal glands (LAD/SAD).

Reformatted images for each adrenal gland were obtained from the cross-sectional images. Parasagittal reconstruction planes containing adrenal glands were progressively modified to oblique, with no curving of the plane until the maximum length of each adrenal gland was reached. The maximum lengths of the adrenal glands then were measured. The lengths of the glands identified as the larger and the smaller gland on reformatted images were designated rLAL and rSAL, respectively. Full sections of each adrenal gland then were reformatted perpendicular to the long axis of the main body of the adrenal gland. The maximum diameters on reformatted views of the larger and smaller glands identified on cross-sectional images were designated rLAD and rSAD, respectively. Ratios (rLAD/Ao, rSAD/Ao, and rADR) analogous to those for the cross-sectional images then were calculated. Additional ratios based on adrenal length, such as the adrenal length ratio (rALR), defined as the ratio of rLAL to rSAL (rLAL/rSAL), and maximum adrenal length divided by Ao for each gland (rLAL/Ao, rSAL/Ao), also were established.

For each adrenal gland, we assessed mural compression and intraluminal invasion of the surrounding vasculature (caudal vena cava, aorta, and renal veins and arteries), as described previously.[30] Intraluminal vascular invasion was defined as the presence of a contrast medium void within a vessel continuous with the adrenal gland. Mural compression was defined as displacement of the vessel wall without luminal invasion. The presence or absence of calcification also was recorded.

Histology

For histological examination, adrenocortical tissue removed surgically or during necropsy was fixed in 10% neutral buffered formalin and embedded in paraffin. Sections were cut and stained with hematoxylin and eosin. Histologic analyses were performed by board-certified pathologists. Adrenal tumors were classified as benign or malignant. Tumor architecture, cell pleomorphism, mitosis frequency, and invasive behavior (ie, capsule or vascular invasion) were recorded. Malignancy was considered in all cases in which at least some evidence of invasive behavior was observed. The functional status of adrenal tumors was considered when atrophy of the adjacent nontumoral adrenocortical tissue was noted.[31]

Data Analysis

Data were analyzed with commercially available software,[j] with the significance level set at 5%. The Shapiro-Wilk *W*-test was used to assess the normality of the data. Data were not normally distributed and therefore described with medians and ranges. Mann-Whitney rank-sum tests were used to compare adrenal measurements between the 2 groups. The thresholds for the most discriminatory parameters were determined from the receiver operating characteristics (ROC) curve. The 95% confidence intervals (CI) for the estimated sensitivity and specificity of these parameters were identified with free software.[k]

Results

Criteria for inclusion in this study were met by 64 dogs. The AIHAC group contained 18 dogs and the ADHAC group contained 46 dogs. Median age at diagnosis was 11 years (range, 7–15 years) for dogs with AIHAC and 11 years (range, 5–15 years) for dogs with ADHAC. The male/female ratio was 10/8 for dogs with AIHAC and 19/27 for dogs with ADHAC. The AIHAC group consisted of 5 Labrador Retrievers, 4 cross-breeds, 2 Fox Terriers, and 7 individuals of other breeds. The ADHAC group consisted of 10 Yorkshire Terriers, 5 Poodles, 4 Boxers, 2 Dachshunds, 2 Bichons, 2 American Staffordshire Terriers, and 2 Labrador Retrievers. The remaining 19 dogs were cross-breeds (5 dogs) and individuals of other breeds.

ACTH stimulation tests were performed in 41 dogs (13 AIHAC and 28 ADHAC) and HAC was confirmed by an abnormal response to ACTH stimulation in 39 dogs (11 AIHAC and 28 ADHAC). The LDDST was performed in 34 dogs (9 AIHAC and 25 ADHAC) and an unsuppressed cortisol concentration 8 hours after dexamethasone injection was observed in 33 of these dogs (8 AIHAC and 25 ADHAC).

ACTH concentration was <5 pg/mL in AIHAC dogs and was between 8 and 500 pg/mL in ADHAC dogs. In 13/18 dogs of the AIHAC group, histologic analysis was possible after adrenalectomy or necropsy, and revealed the presence of a functional adrenal tumor. Carcinoma was diagnosed in 7 dogs and adenoma in the remaining 6 dogs. Six of these 13 dogs (4 dogs with adrenocortical carcinoma and 2 with adenoma) had been included in a previous study.[13] In the 46 ADHAC dogs, 19 dogs displayed feedback inhibition after LDDST, with another 3 dogs displaying suppression after HDDST. Thirteen of these 22 dogs with feedback inhibition were included in the previous study.[13]

The size of the pituitary gland was considered normal in all dogs in the AIHAC group. The pituitary gland was considered enlarged in 20/46 dogs in the ADHAC group. Homogeneous attenuation was noted in 56/64 dogs. In 8 dogs with enlarged pituitary glands, attenuation appeared to be heterogeneous. P/B ratios differed significantly between the AIHAC and ADHAC groups ($P < .01$) with median values (range) of 0.22×10^{-2} (0.15–0.31×10^{-2}) mm^{-1} and 0.27×10^{-2} (0.14–1.35×10^{-2}) mm^{-1}, respectively. In 25/46 ADHAC dogs, P/B ratio values overlapped with the range of P/B ratios for the AIHAC group.

Compression or invasion of blood vessels by adrenal glands was observed only in the AIHAC group. Renal vein compression was identified in 7/18 animals (5/7 right renal vein, 2/7 left renal vein); compression of the caudal vena cava by the right adrenal gland was observed in 5/18 dogs and invasion of the caudal vena cava by the right adrenal gland was observed in 1/18 dogs. Arterial compression also was observed, with the aorta affected in 2/18 cases and the left renal artery affected in 2 other cases. Calcification of 1 of the 2 glands was visible in 10/18 AIHAC dogs and 1/46 ADHAC dogs. In all of these cases, the larger of the adrenal gland was always involved.

In 9 AIHAC dogs (4 carcinomas and 5 adenomas) with vascular compression or invasion, and in 5 AIHAC dogs (4 carcinomas and 1 adenoma) with adrenal calcifications on CT scan images, macroscopic examination during necropsy or surgery, and subsequent histologic analysis were possible. In all of these cases, vascular compression or invasion and adrenal calcification were confirmed.

Measurements of LAD and SAD on cross-sectional CT images and the resulting LAD/Ao, SAD/Ao, and ADR values differed significantly between the AIHAC and ADHAC groups (Table 1 and Figs 1–3). Measurements for AIHAC dogs overlapped with those of ADHAC dogs for 12/18 dogs for LAD and 14/18 dogs for SAD. The calculated ratios for the AIHAC group overlapped with those of the ADHAC group for 12/18 dogs for LAD/Ao, 6/18 dogs for SAD/Ao, and 3/18 dogs for ADR.

Table 1. Measurements and ratios for evaluating the size of the adrenal glands in 46 dogs with ADHAC and in 18 dogs with AIHAC ($P < .05$ considered significant).

	AIHAC		ADHAC		
Measurements	Median	Range	Median	Range	*P*
Cross-sectional images					
LAD	25.0	15.6–68.0	15.0	6.3–29.2	<.001
SAD	6.7	3.3–9.5	12.1	5.4–24.4	<.001
Ao	10.0	6.0–14.1	9.4	4.0–16.0	.347
LAD/Ao	2.4	1.65–4.82	1.55	0.85–3.28	<.001
SAD/Ao	0.63	0.33–1.20	1.33	0.76–1.82	<.001
ADR	3.20	2.26–10.79	1.17	1.01–2.51	<.001
Reformatted images					
rLAD	23.4	13.8–63.0	11.8	5.5–28.8	<.001
rSAD	6.9	3.1–8.8	10.1	5.0–19.6	<.001
rLAL	30.2	15.4–77.2	24.3	10.9–39.7	.143
rSAL	18.9	9.2–27.7	19.8	9.4–38.9	.081
rLAD/Ao	2.23	1.43–4.66	1.30	0.87–2.77	<.001
rSAD/Ao	0.61	0.32–0.84	1.09	0.70–1.83	<.001
rADR	3.70	2.39–11.25	1.14	1.01–2.42	<.001
rLAL/Ao	2.95	1.56–5.84	2.70	1.74–3.47	.263
rSAL/Ao	1.75	0.95–3.14	2.29	1.36–3.13	.001
rALR	1.43	1.17–3.05	1.13	1.01–1.56	<.001

ADHAC, ACTH-dependent hyperadrenocorticism; AIHAC, ACTH-independent hyperadrenocorticism; Ao, aorta diameter; LAD, maximum diameter of the larger adrenal gland; rADR, adrenal diameter ratio on reformatted images; rALR, adrenal length ratio on reformatted images; rLAD, maximum diameter of the larger adrenal gland on reformatted images; rLAL, maximum length of the larger adrenal gland on reformatted images; rSAD, maximum diameter of the smaller adrenal gland on reformatted images; rSAL, maximum length of the smaller adrenal gland on reformatted images; SAD, maximum diameter of the smaller adrenal gland; SAL, maximum length of the smaller adrenal gland.

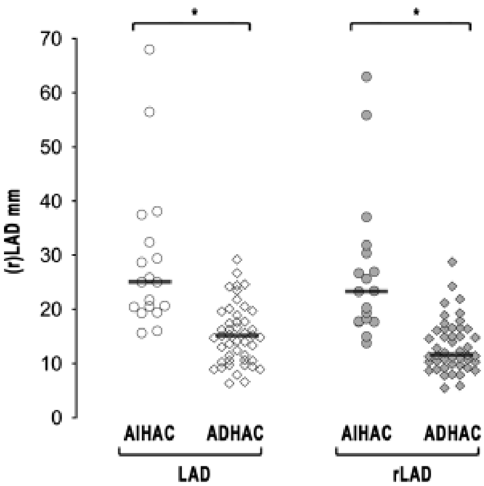

Fig 1. Maximum adrenal diameter of the larger adrenal gland on cross-sectional computed tomography scan views (LAD, open symbols) and reformatted images (rLAD, closed symbols) in dogs with ADHAC (diamonds) and AIHAC (circles). Median values are indicated by horizontal lines (*statistically significant). LAD, maximum diameter of the larger adrenal gland; rLAD, maximum diameter of the larger adrenal gland on reformatted images; ADHAC, ACTH-dependent hyperadrenocorticism; AIHAC, ACTH-independent hyperadrenocorticism.

ROC curve analysis was used to assess the extent to which ADR distinguished between AIHAC and ADHAC. The area under the curve of the ROC curve was 0.994, with a 95% CI of 0.932–1.000. The sensitivity and specificity (95% CI) of ADR for AIHAC detection were 1.000 (0.815–1.000) and 0.956 (0.852–0.995), respectively, for a threshold of 1.95, 0.944 (0.727–0.999) and

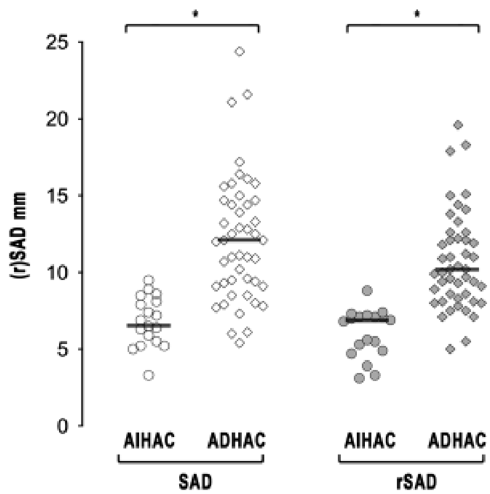

Fig 2. Maximum adrenal diameter of the smaller adrenal gland on cross-sectional computed tomography scan views (SAD, open symbols) and reformatted images (rSAD, closed symbols) in dogs with ADHAC (diamonds) and AIHAC (circles). Median values are indicated by horizontal lines (*statistically significant). SAD, maximum diameter of the smaller adrenal gland; rSAD, maximum diameter of the smaller adrenal gland on reformatted images; ADHAC, ACTH-dependent hyperadrenocorticism; AIHAC, ACTH-independent hyperadrenocorticism.

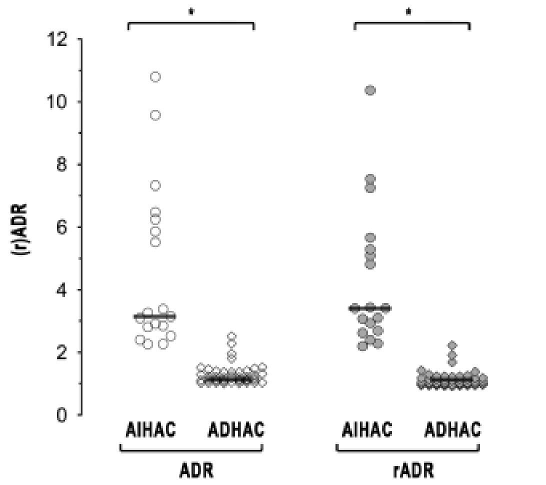

Fig 3. Adrenal diameter ratio (ADR, open symbols) and reformatted adrenal diameter ratio (rADR, closed symbols) in dogs with ADHAC (diamonds) and AIHAC (circles). Median values are indicated by horizontal lines (*statistically significant). ADHAC, ACTH-dependent hyperadrenocorticism; AIHAC, ACTH-independent hyperadrenocorticism.

0.957 (0.852–0.995), respectively, for a threshold of 2.26, and 0.833 (0.586–0.964) and 1.000 (0.923–1.000), respectively, for a threshold of 2.51.

For length-based ratios derived from reformatted images, significant differences between the 2 groups were found only for rSAL/Ao and rALR (Table 1). The rSAL/Ao and rALR values of AIHAC dogs overlapped with those of ADHAC dogs in 15/18 and 10/18 cases, respectively.

On reformatted images, rLAD and rSAD measurements and the values of rLAD/Ao, rSAD/Ao, and rADR obtained differed significantly between the ADHAC and AIHAC groups (Figs 1–3 and Table 1). Both rLAD and rSAD values overlapped with those of the ADHAC dogs in 13/18 AIHAC dogs. An overlap with the values obtained for ADHAC was observed for rLAD/Ao, rSAD/Ao, and rADR, for 12, 6, and 1 of the 18 dogs of the AIHAC group, respectively.

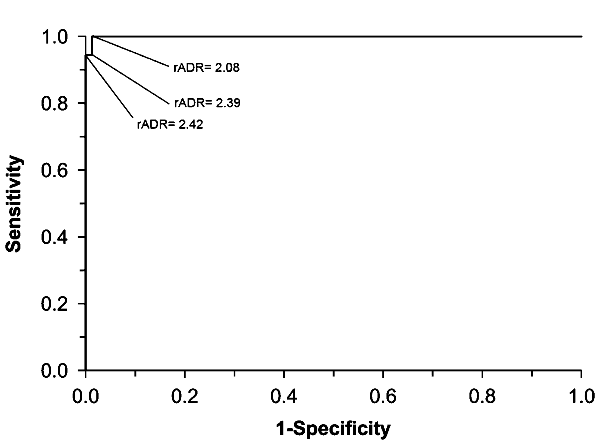

Fig 4. Receiver operating characteristics (ROC) curve, and sensitivity and specificity of 3 selected cutoff values for evaluation of reformatted adrenal diameter ratio (rADR) as a diagnostic test for distinguishing between AIHAC and ADHAC in dogs. ADHAC, ACTH-dependent hyperadrenocorticism; AIHAC, ACTH-independent hyperadrenocorticism.

ROC curve analysis was used to assess the ability of rADR to distinguish between AIHAC and ADHAC (Fig 4). The area under the curve was 0.999, with a 95% CI of 0.942–1.000. The sensitivity and specificity of ADR for AIHAC detection were 1.000 (95% CI, 0.815–1.000) and 0.978 (95% CI, 0.885–0.999), respectively, for a threshold of 2.08, 0.944 (95% CI, 0.727–0.999) and 0.978 (95% CI, 0.885–0.999), respectively, for a threshold of 2.39, and 0.944 (95% CI, 0.727–0.999) and 1.000 (95% CI, 0.923–1.000), respectively, for a threshold of 2.42.

For the 13 AIHAC dogs with available histologic analyses, we evaluated the degree to which measurements of adrenal gland diameter from CT images and the derived ratios distinguished between adrenocortical adenomas and carcinomas. An overlap between benign and malignant tumors was systematically observed for each measurement and ratio considered (Table 2).

Discussion

This study takes advantage of the routine practice of combining pituitary and adrenal CT scans in dogs with

Table 2. Measurements and ratios for evaluating the size of the adrenal glands in 6 dogs with an adrenocortical adenoma and in 7 dogs with an adrenocortical carcinoma ($P < .05$ considered significant).

	Adenomas		Carcinomas		
Measurements	Median	Range	Median	Range	*P*
Cross-sectional images					
LAD	20.6	19.3–29.4	32.4	15.6–68.0	.086
SAD	8.3	3.3–9.5	6.3	5.0–8.6	.116
LAD/Ao	2.38	2.08–3.42	3.75	1.75–4.82	.153
SAD/Ao	0.91	0.33–1.20	0.63	0.45–0.99	.116
ADR	2.83	2.27–6.24	5.86	2.26–10.79	.199
Reformatted images					
rLAD	18.9	15–25.7	30.4	13.8–63	.174
rSAD	5.9	3.3–8.8	5.6	3.9–7.1	.886
rLAL	18.2	15.4–33.0	31.2	18.0–77.2	.086
rSAL	14.0	10.5–25.4	19.2	10.5–27.7	.431
rLAD/Ao	2.17	1.63–3.05	3.19	1.43–4.66	.253
rSAD/Ao	0.80	0.33–0.84	0.59	0.39–0.76	.199
rADR	3.06	2.39–6.15	5.53	2.49–8.18	.253
rLAL/Ao	2.40	1.56–4.06	3.12	2.37–5.48	.116
rSAL/Ao	1.80	1.06–3.14	1.73	1.50–2.39	.886
rALR	1.35	1.24–1.47	2.07	1.24–3.05	.063

Ao, aorta diameter; LAD, maximum diameter of the larger adrenal gland; rADR, adrenal diameter ratio on reformatted images; rALR, adrenal length ratio on reformatted images; rLAD, maximum diameter of the larger adrenal gland on reformatted images; rLAL, maximum length of the larger adrenal gland on reformatted images; rSAD, maximum diameter of the smaller adrenal gland on reformatted images; rSAL, maximum length of the smaller adrenal gland on reformatted images; SAD, maximum diameter of the smaller adrenal gland; SAL, maximum length of the smaller adrenal gland.

HAC at our hospital for retrospective evaluation of the diagnostic accuracy of adrenal gland measurement for differentiating between AIHAC and ADHAC. Sixty-four dogs enrolled at a single center were assigned to the AIHAC and ADHAC groups on the basis of basal plasma ACTH concentration, which is known to have high diagnostic accuracy. In a previous study of a cohort of 109 dogs, we found no overlap between basal plasma ACTH concentrations recorded in dogs with AIHAC and concentrations in dogs with ADHAC.[13] Nineteen dogs were included in both the current study and the previous study. These dogs initially were diagnosed with AIHAC on the basis of histologic examinations of adrenocortical tissue showing functional adrenal tumors, or with ADHAC on the basis of feedback inhibition after DST, with minimal associated risks of allocation errors.

Forty-five dogs were included only in this study (12 with AIHAC and 33 with ADHAC). Additional data, confirming the accuracy of allocation on the basis of plasma ACTH concentration, were available in some of these cases. Adrenocortical histology data were available for 7/12 AIHAC dogs included in this study only, demonstrating the presence of adrenocortical tumors in each case. Similarly, the LDDST was performed in 14/33 ADHAC dogs included in this study only, and feedback inhibition suggested pituitary dependence in 8 of these dogs (95% CI, 30–80%). The sensitivity of this test for ADHAC detection is less than perfect. In the largest study to date evaluating its accuracy, feedback inhibition was identified in 111/181 dogs with ADHAC (95 CI, 54–68%), consistent with our findings.[11] One of the 6 dogs tested by LDDST and displaying no feedback inhibition was subjected to a high-dose DST, and feedback inhibition was observed in this second test.

The size of the pituitary gland was considered normal in 56% (95% CI, 42–70%) of ADHAC dogs and in 100% (95% CI, 85–100%) of AIHAC dogs, limiting the usefulness of pituitary gland examination by CT scan for distinguishing between AIHAC and ADHAC. In a previous report, the pituitary glands of dogs with ADHAC evaluated by CT scan were considered nonenlarged in 39% (95% CI, 28–51%) of dogs, consistent with our findings.[16] Both studies are based on conventional contrast-enhanced CT without dynamic CT. In some ADHAC dogs, despite an absence of pituitary gland enlargement on postcontrast images, pituitary microadenomas can be identified indirectly by dynamic CT scans.[17,32] The accuracy of pituitary gland dynamic CT scan for distinguishing between ADHAC and AIHAC remains to be evaluated.

Only 2 previous studies have evaluated the utility of adrenal gland CT scans for characterizing Cushing's syndrome in dogs: 1 on 9 dogs (AIHAC confirmed in 4) and the other on 10 dogs (AIHAC confirmed in 5).[14,20]

The present survey included 64 dogs with HAC, 18 of which had AIHAC (28%; 95% CI, 18–41%). AIHAC classically is described as accounting for between 15 and 20% of HAC cases.[33] Examination of the records of the included dogs identified no bias that could account for this potential overinclusion of AIHAC cases. The cohort of dogs enrolled in this survey was similar, in terms of age and breed, to those studied in previous surveys.[34–36] The possible predominance of HAC in females remains a matter of debate. Most studies have argued against such a sex-related predisposition, but 1 survey of dogs with AIHAC reported that females accounted for 63% of the dogs included (95% CI, 48–76%).[36–38] The present study did not confirm this trend, with a 95% CI for female representation of 25–66% for AIHAC and of 44–71% for ADHAC.

Animals were included in our study only if a CT scan had been performed before the start of treatment for HAC. Trilostane and mitotane, both used in our institution, are known to induce changes in adrenal gland size.[39–42] Such treatments would therefore bias observations if initiated before the CT scan.

Adrenal gland calcification was observed in both ADHAC (in 1 case only) and AIHAC, confirming ultrasound observations in other studies.[43] Caudal vena cava invasion was observed only in 1 dog with an adrenocortical carcinoma. The sensitivity of CT scan for vascular invasion by adrenal tumors recently has been estimated at 86% (95% CI, 62 to > 99%).[30] The nondetection of a large number of vascular invasions therefore appears unlikely. Vascular invasion seems to be less common in dogs with adrenocortical tumors than in dogs with other adrenal tumors.[30,43,44] Because of this low prevalence, additional CT scan features remain to be identified to predict the aggressiveness of adrenal tumors in cases of HAC. Although assessed in only a small number of dogs, the ability of adrenocortical measurements from CT scan images and derived ratios to discriminate between adrenocortical carcinomas and adenomas would be expected to be low, based on the results reported here. However, present data support the notion that larger glands are more likely to be malignant.[43] Indeed, none of the dogs with an adrenocortical adenoma had a LAD, rLAD, or rLAL above 29.4, 25.7, and 33.0 mm, respectively.

An overlap was observed between the adrenal gland measurements on nonreformatted images of the AIHAC and ADHAC groups, for all of the size parameters studied. In dogs, the long axis of the left adrenal gland is not aligned with either the medial or dorsal plane of the body.[20,45,46] Cross-sectional images therefore generate oblique views of at least 1 adrenal gland rather than transverse views, resulting in variations of apparent gland shape and the possibility of miscalculating maximum diameter and length.[21] In a previous study, attempts were made to identify the largest dorsolateral-to-ventromedial dimension, defined as the "width" and the greatest dimension perpendicular to the width, which was defined as "thickness."[21] Other types of measurement from cross-sectional views also have been described, including measurement of the largest diameter of each adrenal gland.[14] In the absence of data comparing the accuracy and reproducibility of the various methods, we chose to use this last method because of its simplicity.

A major overlap in SAD was observed between the 2 groups, with the dogs in the AIHAC group having an SAD of up to 9.5 mm. This result is not consistent with the findings of a recent study demonstrating the usefulness of ultrasound measurements for distinguishing between AIHAC and ADHAC in dogs with equivocal adrenal asymmetry, in which the maximal dorsoventral diameter of the smaller adrenal gland was considered to give accurate results with a threshold of 5.0 mm. There are many possible reasons for this discrepancy, including differences in recruitment between these 2 studies. The measurements themselves also differed, with SAD not always being dorsoventral in the present study. Moreover, different imaging techniques may give discordant results for adrenal gland measurement.[47] The concordance between adrenal gland measurements on CT and ultrasound scans in dogs has never been assessed, making it difficult to compare the 2 modalities. Finally, the accuracy of CT scans for measuring adrenal glands remains unclear. CT scan measurement was reported to result in both over- and underestimation of adrenal gland size with respect to direct measurements of excised normal, hyperplastic, and tumoral adrenal glands in 1 study.[20] In another study, a correlation was found between CT measurements and gross measurement of normal adrenal glands.[21] However, the slope of the regression line was <1, indicating that CT scan measurements underestimated gland measurements >10.0 mm, and overestimated measurements <10.0 mm. Because all 18 SAD measurements in the AIHAC group and 16/46 SAD measurements in the ADHAC group were <10.0 mm, this parameter may have been particularly affected by a possible bias in size estimation. The reasons for this possible bias remain unclear, but partial volume effects may play a role in such small structures,[48] despite the use of thin slices to limit this artifact.

A previous study indicated that a maximal dorsoventral thickness >20.0 mm on ultrasound scan was more likely to reflect the presence of an adrenal tumor than hyperplasia.[43] However, exceptions have been described, with maximal dorsoventral thickness in some cases of adrenal hyperplasia reaching up to 35.0 mm.[31] Our CT-based study confirmed that the maximum diameter of the larger gland may sometimes exceed 20.0 mm in dogs with ADHAC, for measurements on cross-sectional or reformatted views (9/46 for LAD and 4/46 for rLAD).

The standardization of (r)SAD and (r)LAD, by dividing by Ao, to take into account differences in the sizes of the dogs examined, resulted in no clinically relevant decrease in the overlap between the AIHAC and ADHAC groups for the various parameters.

Thus, evaluation of the degree of asymmetry between the adrenal glands by calculating adrenal gland maximum diameter ratios is a valuable method for distinguishing between AIHAC and ADHAC. The utility of adrenal gland symmetry or asymmetry on cross-sectional CT views for determining etiological diagnosis was considered in 2 previous studies.[14,20] However, asymmetry was defined subjectively in these studies and no cut-off point was proposed for distinguishing between etiologies of HAC. The present study confirms that a certain degree of asymmetry may be observed in dogs with ADHAC, highlighting the need for validated objective criteria defining the degree of asymmetry required for AIHAC diagnosis. Indeed, in the 2 previous studies, 1/9 and 1/10 cases initially were identified as AIHAC on the basis of adrenal gland asymmetry, but adrenocortical hyperplasia subsequently was identified on adrenalectomy, suggesting a diagnosis of ADHAC.[14,20] Based on the adrenal gland measurements available for one of these studies, an ADR of 1.42 was calculated for the dog with dubious adrenal asymmetry, this value being within the range for ADHAC dogs in this survey, but below the range for AIHAC dogs.[20]

Adrenal gland maximum diameter ratio differed significantly between the AIHAC and ADHAC groups, whether derived from cross-sectional CT images (ADR) or from reformatted images (rADR). However, the overlap between the ranges of values obtained for AIHAC and ADHAC was more limited for rADR. These data suggest that measurements from reformatted images, although more time consuming to obtain, more accurately distinguish between the 2 conditions.

Because animals were assigned to groups in this study on the basis of plasma ACTH concentration, the HAC of dogs allocated to the AIHAC group may have been because of either functional adrenal tumor or ACTH-independent adrenocortical hyperplasia. This second cause of AIHAC has been reported only once in a veterinary publication, in the context of food-dependent HAC.[4] This is the only known case of its type, and it is highly likely that all the cases included in this survey were because of functional adrenal tumors, even in the dogs for which no histological data were available. The accuracy of rADR for AIHAC discrimination in cases of ACTH-independent adrenocortical hyperplasia remains to be determined and will require the identification of other cases of the new entity. However, in the aforementioned case of food-dependent HAC, the adrenal glands on CT images were described as symmetric and would certainly have been misclassified if the rADR threshold validated here had been used.[4] Likewise, bilateral functional adrenal tumor, although rare, may generate equivocal images characterized by a certain degree of adrenal symmetry, resulting in possible misclassification by rADR.

These possible exceptions aside, the present study demonstrates that rADR is an accurate tool for distinguishing between AIHAC and ADHAC. The most sensitive cut-off point tested in this study (2.08) appears to be the most relevant, because of the clinical implications of misclassifying a dog with AIHAC as having ADHAC. In field conditions, given the relatively low frequency of AIHAC in dogs, a simple ratio of the maximum diameters of the adrenal glands can be used to rule out the presence of functional adrenal tumors in cases in which $rADR \leq 2.08$, with a high degree of confidence.

In conclusion, this study evaluated the utility of various measurements of adrenal gland size and derived ratios obtained from CT scans, for distinguishing between AIHAC and ADHAC in a large number of dogs with HAC. Maximum adrenal gland diameter ratio appeared to be the most useful parameter, particularly when this ratio was calculated from reformatted images. A $rADR \leq 2.08$ is highly suggestive of ADHAC.

Footnotes

[a] Enzymun-Test cortisol, Roche Diagnostics, Meylan, France
[b] Synacthène injectable, tetracosactide, 0.25 mg/mL, Novartis Pharma SA, Rueil-Malmaison, France
[c] Dexadreson, dexamethasone phosphate, 2 mg/mL, Intervet-Schering Plough, Beaucouzé, France
[d] Siemens Medical Solutions Diagnostics, Los Angeles, CA
[e] Rapinovet, Schering-Plough Vétérinaire, Levallois-Perret, France
[f] Isoflurane aerrane, Baxter SAS, Maurepas, France
[g] Télébrix 35, sodium and meglumine ioxitalamate, 350 mg of iodine/mL, Laboratoire Guerbet, Roissy-Charles-de-Gaulle, France
[h] Scanner Hispeed CT/e Plus, General Electric Medical Systems, Milwaukee, WI
[i] Advantage Workstation, AW 4.4. General Electric Medical Systems
[j] SPSS Statistical Package, version 16.0, SPSS Inc, Chicago, IL
[k] Measuring usability: confidence interval calculator for a completion rate (http://www.measuringusability.com/wald.htm)

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