


Standard Article

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Evaluation of Renal Perfusion in Hyperthyroid Cats before and after Radioiodine Treatment

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Background: Hyperthyroidism and chronic kidney disease (CKD) are common in elderly cats. Consequently, both diseases often occur concurrently. Furthermore, renal function is affected by thyroid status. Because changes in renal perfusion play an important role in functional renal changes in hyperthyroid cats, investigation of renal perfusion may provide novel insights.

Objectives: To evaluate renal perfusion in hyperthyroid cats with contrast-enhanced ultrasound (CEUS).

Animals: A total of 42 hyperthyroid cats was included and evaluated before and 1 month after radioiodine treatment.

Methods: Prospective intrasubject clinical trial of contrast-enhanced ultrasound using a commercial contrast agent (SonoVue) to evaluate renal perfusion. Time-intensity curves were created, and perfusion parameters were calculated by off-line software. A linear mixed model was used to examine differences between pre- and post-treatment perfusion parameters.

Results: An increase in several time-related perfusion parameters was observed after radioiodine treatment, indicating a decreased blood velocity upon resolution of the hyperthyroid state. Furthermore, a small post-treatment decrease in peak enhancement was present in the renal medulla, suggesting a lower medullary blood volume.

Conclusions and Clinical Importance: Contrast-enhanced ultrasound indicated a higher cortical and medullary blood velocity and higher medullary blood volume in hyperthyroid cats before radioactive treatment in comparison with 1-month post-treatment control.

Key words: Contrast-enhanced ultrasound; Feline; Hyperthyroidism; Kidney.

Both hyperthyroidism and renal disease are common in elderly cats, and not surprisingly, these diseases often occur concurrently. The prevalence of cats suffering from both diseases has been reported to be approximately 14%.¹ The incidence of azotemia shortly after treatment of hyperthyroidism even reaches 40% suggesting unmasking of pre-existing impaired renal function.^{1–3} A complex relationship exists between the thyroid glands and the kidneys. In cats with hyperthyroidism, increased serum thyroxine concentrations induce decreased vascular resistance as well as increased cardiac output, leading to increased renal blood flow, and subsequently an increased glomerular filtration rate (GFR).⁴ Treatment of hyperthyroidism inversely results in a decrease in GFR 1 month after treatment, whereas GFR is found to be

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Abbreviations:

AUC	area under the curve
bpm	beats per minute
CEUS	contrast-enhanced ultrasound
CKD	chronic kidney disease
EDTA	ethylenediaminetetraacetic acid
FT	fall time
GFR	glomerular filtration rate
mTT	mean transit time
PE*	peak enhancement normalized to interlobar artery
PE	peak enhancement
ROI	region of interest
RT	rise time
sCr	serum creatinine
TSH	thyroid-stimulating hormone
TT4	total thyroxine
TTP	time to peak
UPC	urinary protein:creatinine ratio
USG	urine specific gravity
WiAUC	wash-in area under the curve
WiPI	wash-in perfusion index
WiR	wash-in rate
WoAUC	wash-out area under the curve
WoR	wash-out rate

stable between 1 and 6 months post-treatment.^{2,5} Importantly, predicting changes in renal function before treatment of hyperthyroidism is complicated. Routine renal variables such as serum creatinine concentration, serum urea concentration, urine specific gravity, and proteinuria are insensitive because they are strongly influenced by the hyperthyroid state of the cat.⁴ Pretreatment measurement of GFR shows promise in predicting post-treatment azotemia, but substantial overlap exists with cats that remain nonazotemic.^{2,4} Therefore, an ideal test to predict post-treatment azotemia currently is not available.

Renal blood flow plays a fundamental role in the functional renal changes present in hyperthyroid cats; hence, evaluation of renal perfusion could provide important new insights into renal function in hyperthyroid cats. However, performing an accurate, noninvasive measurement of renal perfusion is challenging. Contrast-enhanced computed tomography, magnetic resonance imaging, and renal scintigraphy can provide information about macroperfusion.^{6–8} However, their use in clinical practice is limited by equipment availability, involvement of ionizing radiation, use of nephrotoxic contrast agents, or some combination of these.^{6–8} Contrast-enhanced ultrasound is a functional ultrasound modality that allows assessment of both macro- and microperfusion by use of an IV-administered contrast agent. The contrast agent consists of gas-filled microbubbles stabilized by an outer phospholipid shell that is approximately the size of red blood cells. Consequently, they do not cross the endothelium and act as blood pool agents. Major advantages associated with CEUS are its excellent safety profile allowing use in geriatric patients and patients suffering from renal disease, noninvasive nature, absence of ionizing radiation, and relatively short imaging times.⁹ In human medicine, CEUS has been shown to be useful in the diagnosis of patients with allograft rejection, diabetic nephropathy, and chronic renal disease.^{10–14} In dogs, CEUS was capable of detecting perfusion changes in iatrogenically induced ischemic renal disease and iatrogenic hypercortisolism.^{15,16} Promising results also have been obtained in cats, in which, renal vasoconstriction induced by angiotensin II infusion could be detected by CEUS but not by renal scintigraphy.¹⁷

The objective of our study was to evaluate renal perfusion with CEUS in hyperthyroid cats before and after radioiodine treatment. The hypothesis was that higher renal perfusion, both higher blood velocity and higher blood volume, would be present before radioiodine treatment compared to the 1-month post-treatment control.

Materials and Methods

Fifty-one client-owned hyperthyroid cats presented for radioiodine treatment at the Faculty of Veterinary Medicine of Ghent University (Belgium) were included in the study with the permission of the local ethical committee of Ghent University (EC 2015/67). Owners signed an informed consent form before inclusion.

Inclusion criteria were a diagnosis of hyperthyroidism based on clinical signs, increased serum total thyroxine concentration (TT4) based on the references range of 10–30 nmol/L, and increased pertechnetate uptake in 1 or both thyroid glands on scintigraphic scan. Cats with concurrent systemic disease (including pre-existing overt renal disease) or with clinically relevant cardiac disease (defined as severe left atrial dilatation, signs of congestive heart failure, or clinically relevant arrhythmias) were excluded. Antithyroid medication (methimazole, carbimazole) or iodine-restricted diet^a was discontinued at least 10 days before radioiodine treatment. Cats maintained their original diet throughout the study period. Cats receiving a homemade diet or diets based on raw meat were excluded.

The cats were evaluated on the day of radioiodine treatment and 1 month after treatment (mean, 32 days after treatment; range, 25–43 days). Pretreatment evaluation included a thorough

physical examination, standard 2-view thoracic radiographs (lateral and ventrodorsal projections), abdominal ultrasound examination, CEUS of the kidneys, and cardiac ultrasound examination. Post-treatment evaluation included physical examination, CEUS of the kidneys, and cardiac ultrasound examination. A CBC, serum biochemistry profile including serum TT4, and complete urinalysis (urine specific gravity, urinary pH, urinary protein:creatinine ratio, sediment examination,¹⁸ and bacterial culture) were performed on both occasions. On both occasions, systolic blood pressure was measured by Doppler ultrasonic technique, following the consensus statement of the American College of Veterinary Internal Medicine.¹⁹ Physical examination and blood pressure measurement were performed before the other examinations and after an acclimatization period.

In 10 of 42 cats, GFR was measured using a plasma exogenous creatinine clearance test. This test was performed 1 day before radioiodine treatment and repeated 1 day before the post-treatment examination. A limited sampling strategy, minimally impacting the reliability of the GFR estimate, was used, as previously described.²⁰ Briefly, 40 mg/kg creatinine was administered IV and blood samples were taken in EDTA tubes before and 5, 30, 60, 120, 180, 360, and 600 minutes after injection. The borderline GFR cutoff value was defined as 1.7 mL/min/kg, the lower GFR cutoff value as 1.2 mL/min/kg.²⁰

The cats were treated with an individually adapted dose of radioiodine (¹³¹I) injected IV, after the previously described examinations. The dose was based on the severity of the clinical signs, serum TT4, and thyroid-to-salivary gland ratio as determined on the pertechnetate scan, as described previously.²¹ The mean dose administered was 146,99 MBq (range, 67,71–455,10 MBq).

CEUS Procedure

A 22-gauge indwelling catheter was placed in the cephalic vein. Anesthesia was induced with a bolus of propofol,^b 3.5–7.7 mg/kg IV given to effect, and maintained with 0–3 additional boluses as necessary to cover the total duration of the study lasting approximately 15 minutes. Anesthesia was used for both the pre- and post-treatment CEUS examination.

The hair was clipped over the ventrolateral aspect of the abdomen, and coupling gel was applied to the skin. The ultrasound examinations were performed with the cat in dorsal recumbency. The kidney of interest was centered on the screen and was imaged in a longitudinal plane using dual-screen (simultaneous display of conventional B-mode and contrast-mode images). The transducer was manually positioned during each imaging procedure and was maintained at the same position during the CEUS examination.

The contrast agent,^c 0.05 mL/kg, was injected IV (bolus injection over \pm 3 s) followed by injection of a 1.5 mL saline bolus. A 3-way stopcock was used to avoid any delay between the injection of contrast agent and saline. The same person performed the injection in a standardized way. Three injections of contrast were performed: 2 for the left kidney and 1 for the right kidney. The first injection was not used for further analysis because it results in lower enhancement compared to subsequent injections.²² Between subsequent injections, to avoid artifacts, remnant microbubbles were completely destroyed by setting the acoustic power at the highest level and scanning the caudal aspect of the abdominal aorta for approximately 2 minutes.

All examinations were performed with a linear transducer of 12–5 MHz on a dedicated machine^d with contrast-specific software. Basic technical variables were a single focus placed under the kidney, persistency off, mechanical index 0.09, high dynamic range setting (C50), timer started at the beginning of the injection, and gain 85% (corresponding to a nearly dark/anechoic image

before contrast administration). The settings were repeated during each injection. All studies were digitally registered as a movie clip at a rate of 9 frames per second, for 90 seconds.

The clips were exported in DICOM format and analyzed off-line by specialized computer software^e for objective quantitative analysis. Six regions-of-interest (ROIs) were manually drawn: 3 in the renal cortex, 2 in the renal medulla, and 1 on an interlobar artery. The ROIs were similar in size and drawn at the same depth for every region (Fig 1). For every ROI, the software determined mean pixel intensity as a function of time and created a time-intensity curve. Time-intensity curves were analyzed for peak enhancement (PE), wash-in area under the curve (WiAUC), rise time (RT), mean transit time (mTT), time to peak (TTP), wash-in rate (WiR), wash-in perfusion index (WiPI; WiAUC/RT), wash-out area under the curve (WoAUC), total area under the curve (AUC), fall time (FT), and wash-out rate (WoR). The PE corresponds to the maximum contrast medium signal intensity. The WiAUC is calculated as the sum of all amplitudes inside the range from the beginning of the curve up to the TTP. Similarly, WoAUC corresponds to the sum of all amplitudes inside the range from the TTP to the end of the descending curve. The other parameters, that is, RT, mTT, TTP, WiR, WiPI, FT, and WoR, are related to blood velocity. The WiR and WoR represent the maximum and minimum slopes of the time-intensity curves. The RT corresponds to the time interval between the first arrival of contrast and the time of peak intensity. The FT, in contrast, is the duration of contrast wash-out. Mean transit time is the mean duration of complete contrast medium perfusion. The values for the 3 ROIs in the renal cortex and 2 ROIs in the renal medulla were averaged. Peak enhancement, for the cortex and medulla, was normalized to the values obtained for the interlobar artery (PE*).

Statistical Analysis

Analyses^f were based on a linear mixed model with cat and kidney nested in cat as random effects and treatment (pre/post-radioiodine treatment) as a categorical fixed effect. Analyses were performed separately for the renal cortex and medulla. Correlations between perfusion parameters and heart rate, blood pressure, serum TT4, sCr, and GFR were calculated for the renal cortex and medulla using Spearman correlation coefficients (ρ). A difference was considered statistically significant if $P < 0.05$.

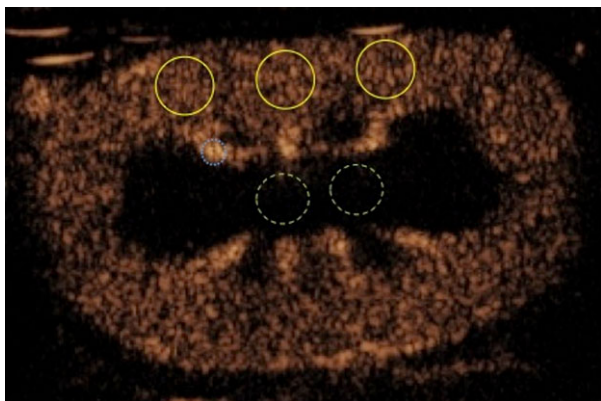


Fig 1. Contrast-enhanced ultrasound image of the left kidney of a cat illustrating the position of the regions-of-interest in the renal cortex (yellow \bigcirc), renal medulla (green ---), and interlobar artery (blue +++). The image was obtained at peak cortical enhancement (10 seconds after contrast injection).

Results

In total, 9 cats were excluded from the study: 4 cats because of additional pathology (suspected pulmonary neoplasia, $n = 1$; intestinal lymphoma, $n = 1$; severe cardiomegaly and left atrium dilatation, $n = 1$; second-degree atrioventricular block, $n = 1$), 4 cats because of aggressive behavior, and 1 cat was lost for follow-up. For the 42 remaining cats, no clinically relevant abnormalities were noted on thoracic radiographs or abdominal ultrasound examination. Echocardiographic changes were compatible with hyperthyroidism (left ventricular hypertrophy, mild-to-moderate left atrial dilatation) and improved after treatment of hyperthyroidism in most cases.

Breed distribution consisted of 40 domestic short- or long-haired cats, 1 British Shorthair, and 1 Chartreux. Twenty-three cats were female neutered, and 19 were male neutered. The median age at time of inclusion was 12 years 9 months (range, 7 years 5 months to 16 years 7 months).

Of the 42 cats included, 27 (64%) had post-treatment serum TT4 within the normal reference interval, and 15 (36%) has serum TT4 value below normal. None had serum TT4 above the normal reference interval at 1 month after radioiodine treatment. Two cats (4.8%) developed post-treatment azotemia, 1 of them had serum TT4 below the reference range 1-month post-treatment. Additionally, 2 cats with normal sCr had decreased post-treatment GFR. An overview of the baseline characteristics of the cats, before and after radioiodine treatment, is provided in Table 1.

Both kidneys had normal appearance on B-mode ultrasonography in 27 cats, including 1 of the 2 cats that developed post-treatment azotemia. Two cats (5%) had a unilateral small kidney (<3 cm), with subjectively decreased corticomedullary definition, 1 of these developed post-treatment azotemia, whereas the other did not. Three (7%) other cats had mildly decreased corticomedullary definition in normal-sized kidneys. Three cats (7%) had mildly irregular renal outlines, 5 (12%) had segmental cortical lesions, and 4 (10%) had small

Table 1. Clinical variables before and 1 month after radioiodine treatment provided as mean \pm standard deviation (bpm beats per minute; TT4 total thyroxine; USG urine specific gravity; UPC urinary protein: creatinine ratio; GFR glomerular filtration rate)

Variables	Pretreatment	Post-treatment	<i>P</i> -value
Body weight (kg)	3.8 \pm 0.7	4.1 \pm 0.7	<0.001
Heart rate (bpm)	209.4 \pm 27.2	169.7 \pm 28.5	<0.001
Blood pressure (mmHg)	161.2 \pm 29.8	162.7 \pm 31.8	0.793
TT4	114.6 \pm 27.9	13.0 \pm 27.9	<0.001
sCr (μ mol/L)	65.3 \pm 26.6	109.6 \pm 26.6	<0.001
Serum urea (mmol/L)	8.7 \pm 3.2	10.4 \pm 3.2	<0.001
USG	1.044 \pm 0.006	1.037 \pm 0.006	<0.001
UPC	0.71 \pm 0.32	0.23 \pm 0.32	<0.001
GFR (mL/kg/min)	3.6 \pm 1.9	2.1 \pm 1.9	0.003

cystic lesions, none of these cats developed post-treatment azotemia. One cat (2%), without post-treatment azotemia, had mild bilateral pyelectasia without signs of obstruction, which improved post-treatment. Eight cats (19%) had bilateral hyperechoic renal cortices, and all of them were castrated males, suggesting fat infiltration.²³

No clinically relevant adverse effects of the sonographic contrast material were noted. However, 1 cat experienced mild and transient tachypnea after the first injection of contrast agent during the pretreatment evaluation, which resolved spontaneously within 10 minutes.

Several perfusion parameters showed significant changes between pre- and post-treatment values. A comparison between the perfusion parameters before and after radioiodine treatment is provided in Table 2. Moreover, representative time-intensity curves are provided in Figure 2.

The RT ($P < 0.001$), mTT ($P = 0.011$), TTP ($P < 0.001$), and FT ($P < 0.001$) for the renal cortex increased significantly post-treatment. In parallel, the WiR ($P = 0.008$) and WoR ($P = 0.004$) decreased. A post-treatment increase also was seen for the WiAUC ($P < 0.001$), WoAUC ($P < 0.001$), and total AUC ($P < 0.001$) for the renal cortex. Similarly, for the renal medulla, RT ($P = 0.001$) and TTP ($P < 0.001$) increased post-treatment, whereas WiR ($P = 0.004$) decreased. Moreover, a significant post-treatment decrease in

Table 2. Mean \pm standard deviation values of renal perfusion parameters in hyperthyroid cats before and 1 month after radioiodine treatment.

Variable, by location	Pretreatment	Post-treatment	<i>P</i> -value
Renal cortex			
PE	2193.27 \pm 958.18	2146.47 \pm 958.18	0.771
PE*	20.09 \pm 9.59	19.06 \pm 9.59	0.557
WiAUC	3566.26 \pm 1751.87	4864.32 \pm 1751.87	<0.001
RT	2.79 \pm 0.66	3.79 \pm 0.66	<0.001
mTT	24.36 \pm 10.37	28.73 \pm 10.37	0.011
TTP	7.83 \pm 1.43	9.91 \pm 1.43	<0.001
WiR	1119.38 \pm 553.84	793.75 \pm 553.84	0.008
WiPI	1342.53 \pm 584.95	1317.72 \pm 584.95	0.801
WoAUC	4830.39 \pm 2389.00	6767.46 \pm 2389.00	<0.001
AUC	8396.54 \pm 4124.15	11632.00 \pm 4124.15	<0.001
FT	3.87 \pm 1.10	5.46 \pm 1.10	<0.001
WoR	755.90 \pm 407.57	501.47 \pm 407.57	0.004
Renal medulla			
PE	308.93 \pm 162.93	270.59 \pm 165.39	0.093
PE*	3.01 \pm 1.68	2.37 \pm 1.68	0.044
WiAUC	2530.39 \pm 1312.61	2512.68 \pm 1334.13	0.935
RT	14.01 \pm 4.28	16.25 \pm 4.41	0.001
mTT	68.36 \pm 70.83	87.84 \pm 72.52	0.196
TTP	24.58 \pm 4.93	30.99 \pm 4.99	<0.001
WiR	36.90 \pm 24.82	27.40 \pm 25.15	0.004
WiPI	194.04 \pm 101.36	168.53 \pm 102.85	0.075
WoAUC	4403.78 \pm 2352.51	3974.35 \pm 2403.64	0.259
AUC	6949.01 \pm 3629.28	6442.36 \pm 3708.28	0.387
FT	25.54 \pm 8.55	26.80 \pm 8.75	0.386
WoR	18.98 \pm 14.65	15.28 \pm 14.91	0.072

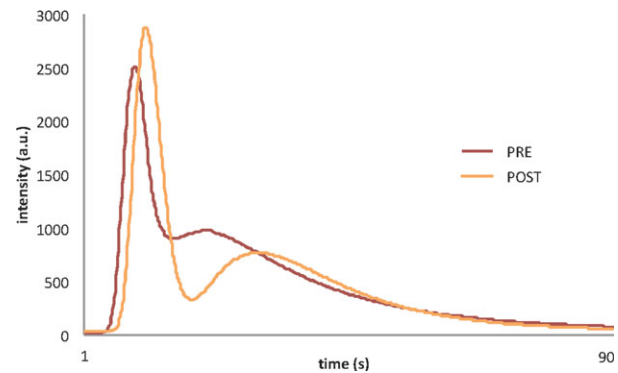


Fig 2. Representative time-intensity curves for the renal cortex of a hyperthyroid cat before and 1 month after radioiodine treatment.

normalized PE (PE*; $P = 0.044$) was observed for the medulla.

Significant negative correlations were present between heart rate and RT in the cortex ($\rho = -0.46$; $P < 0.001$), and TTP for both cortex ($\rho = -0.42$; $P = 0.001$) and medulla ($\rho = -0.39$; $P = 0.003$), meaning that shorter TTP and RT, and thus higher renal blood velocity, were present as heart rate increased. Similarly, significant negative correlations were found between serum TT4 and cortical RT ($\rho = -0.60$; $P < 0.001$), TTP ($\rho = -0.59$; $P < 0.001$) and FT ($\rho = -0.57$; $P < 0.001$), and medullary TTP ($\rho = -0.48$; $P < 0.001$). Moreover, a positive correlation was found between sCr and cortical ($\rho = 0.68$; $P < 0.001$) and medullary ($\rho = 0.41$; $P = 0.001$) TTP, and cortical FT ($\rho = 0.52$; $P < 0.001$). Negative correlations were found between GFR and cortical TTP ($\rho = -0.51$; $P = 0.021$), cortical RT ($\rho = -0.53$; $P = 0.002$), cortical FT ($\rho = -0.50$; $P = 0.024$), and medullary RT ($\rho = -0.62$; $P = 0.004$) and FT ($\rho = -0.68$; $P = 0.001$).

Significant correlations also were present between heart rate and sCr ($\rho = -0.48$; $P < 0.001$), heart rate and GFR ($\rho = 0.47$; $P = 0.042$), heart rate and serum TT4 ($\rho = 0.59$; $P < 0.001$), serum TT4 and sCr ($\rho = -0.71$; $P < 0.001$), and serum TT4 and GFR ($\rho = 0.61$; $P = 0.004$), complicating the interpretation. There was no significant difference in pre- and post-treatment blood pressure.

Discussion

Several studies have investigated routine urine and serum renal markers and GFR in hyperthyroid cats before and after treatment.^{2,3,5,24-27} Ours is the first study to focus on renal perfusion. Evaluation of renal blood flow is of major interest because the changes in perfusion are known to cause changes in GFR and may therefore precede the effect on GFR.⁴

Contrast-enhanced ultrasound was able to detect significant changes in renal blood flow before and after radioiodine treatment. A faster inflow of contrast agent, reflected by lower RT and TTP, was present during the hyperthyroid state. Similarly, a faster outflow (FT) was

present. Consequently, the time of duration of contrast enhancement (mTT) was shorter. The WiR and WoR, representing the slope of, respectively, the inflow and outflow phases of the time-intensity curve, were higher in the pretreatment phase. The combination of these findings indicates a higher velocity of renal blood flow in hyperthyroid cats, which decreases significantly 1 month after ¹³¹I treatment. Similar changes were present for the renal medulla. The changes in CEUS parameters can in part be attributed to the decreased systemic vascular resistance that is present in hyperthyroidism. Thyroid hormones induce increased nitric oxide concentrations in the renal cortex and medulla, resulting in vasodilatation. Additionally, an increased number of beta-adrenergic receptors is present in the renal cortex during the hyperthyroid state.⁴ Secondly, the ultrasound contrast agent is injected IV and hence travels in the systemic circulation before reaching the kidney. Therefore, the higher heart rate and cardiac output in hyperthyroid cats will have reinforced the effects on renal blood velocity. This also is reflected by the moderate negative correlations between heart rate and several time-based perfusion parameters.

The AUC of the renal cortex significantly increased after radioiodine treatment. The AUC is influenced by both the height of the time-intensity curve (intensity, represented by the PE) and the width of the curve (time, represented by several time-based parameters, most importantly mTT). No significant changes were observed in PE after radioiodine treatment. Therefore, the change in AUC can be attributed to the longer duration of contrast enhancement after radioiodine treatment.

Although most of the previously mentioned data were obtained in the renal cortex, little is known about the microvascular alterations accompanying hyperthyroidism in the renal medulla. Our study showed a small, but significant decrease in normalized PE (PE*) for the renal medulla after radioiodine treatment indicating a larger blood volume in the renal medulla during the hyperthyroid state. The hyperthyroid state induces increased renal blood flow, resulting from a combination of increased cardiac output, decreased vascular resistance, overall increased blood volume, and upregulation of beta-adrenergic receptors in the renal cortex.^{4,28} A higher estimated renal blood flow in hyperthyroid cats has been described previously.²⁹ In that study, total renal blood flow was measured using a radionuclide based technique (¹³¹I ortho-iodo-hippurate). Nevertheless, no significant changes were observed in PE for the renal cortex in our study, although they were expected. This finding is most likely caused by the high variability and consequently broad 95% confidence intervals for this parameter.^{30,31} The intensity measured on CEUS images, and thus the PE, is strongly influenced by several factors. Uncontrollable patient-related factors such as filtration by the lungs and phagocytosis by the reticuloendothelial system will influence the final microbubble concentration in the renal parenchyma.^{32,33}

Only, 4.8% of the cats in our study developed post-treatment azotemia, which is considerably lower than the 17–39% reported in literature.^{1,2,25,26} The percentage of cats having serum TT4 below the reference interval 1 month after radioiodine treatment (36%) was similar to values reported in literature (24–51%).^{24,34,35} Iatrogenic hypothyroidism is well known to contribute to the development of renal dysfunction.³⁵ On the other hand, CKD can induce euthyroid sick syndrome with suppression of serum TT4. Measurement of thyroid-stimulating hormone (TSH) allows differentiation between iatrogenic hypothyroidism and euthyroid sick syndrome. The combination of low TT4 and high TSH is consistent with iatrogenic hypothyroidism.^{4,28} However, TSH concentration also is influenced by radioiodine treatment, and TSH concentration is reported to be within normal reference interval 3 months after radioiodine treatment.³⁵ Thyroid stimulating hormone was not measured in our study.

Because of the low number of cats developing CKD after radioiodine treatment in our study, it was not possible to assess the predictive value of CEUS for the development of post-treatment azotemia. Longer follow-up might have allowed identification of additional cats developing CKD, but significant changes in renal function are reported to occur within 4 weeks after treatment and not thereafter.^{2,5}

Contrast-enhanced ultrasound is a short, nonpainful procedure and thus sedation or anesthesia usually is not necessary. However, to perform accurate quantification afterward, it is mandatory that the animals remain immobile during the acquisition of the CEUS clip. Taking into account that hyperthyroid cats often are hyperactive, stress intolerant and even aggressive, anesthesia may be required in some hyperthyroid cats. Propofol anesthesia may influence CEUS parameters, causing a delay in TTP and a slower wash-in of contrast agent.³⁶ Therefore, to compare the perfusion parameters, it was necessary to use anesthesia in all cats, both before and after radioiodine treatment. In our study, heart rate, blood pressure, and cardiac output were not evaluated during the period of anesthesia. Therefore, the hemodynamic influence of the anesthetic agent could not be evaluated.

In conclusion, CEUS allowed assessment of renal perfusion in hyperthyroid cats before and after radioiodine treatment. A significant decrease in both cortical and medullary blood velocity was noted 1 month after radioiodine treatment. However, no significant decrease in blood volume could be detected in the renal cortex, whereas a post-treatment decrease in normalized PE was observed in the renal medulla.

Footnotes

^a Hill's Prescription Diet Y/D, Hill's Pet Nutrition, Topeka, Kansas

^b Propofol, Abbott Laboratories, Chicago, Illinois

^c SonoVue, Bracco, Milan, Italy

^d iU22, Philips, Amsterdam, The Netherlands

^e VueBox, Bracco Suisse SA, Geneva, Switzerland

^f SAS version 9.4, SAS Institute Inc, Cary, North Carolina

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

- Milner RJ, Channell CD, Levy JK, et al. Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996–2003). *J Am Vet Med Assoc* 2006;228:559–563.
- van Hoek I, Lefebvre HP, Peremans K, et al. Short- and long-term follow-up of glomerular and tubular renal markers of kidney function in hyperthyroid cats after treatment with radioiodine. *Domest Anim Endocrin* 2009;36:45–56.
- Slater MR, Geller S, Rogers K. Long-term health and predictors of survival for hyperthyroid cats treated with iodine 131. *J Vet Intern Med* 2001;15:47–51.
- van Hoek I, Daminet S. Interactions between thyroid and kidney function in pathological conditions of these organ systems: A review. *Gen Comp Endocr* 2009;160:205–215.
- Boag AK, Neiger R, Slater L, et al. Changes in the glomerular filtration rate of 27 cats with hyperthyroidism after treatment with radioactive iodine. *Vet Rec* 2007;161:711–715.
- Daniel GB, Mitchell SK, Mawby D, et al. Renal nuclear medicine: A review. *Vet Radiol Ultrasoun* 1999;40:572–587.
- Herget-Rosenthal S. Imaging techniques in the management of chronic kidney disease: Current developments and future perspectives. *Semin Nephrol* 2011;31:283–290.
- Grenier N, Cornelis F, Le Bras Y, et al. Perfusion imaging in renal diseases. *Diagn Interv Imaging* 2013;94:1313–1322.
- Ohlerth S, O'Brien RT. Contrast ultrasound: General principles and veterinary clinical applications. *Vet J* 2007;174:501–512.
- Dong Y, Wang WP, Cao J, et al. Early assessment of chronic kidney dysfunction using contrast-enhanced ultrasound: A pilot study. *Brit J Radiol* 2014;87:1–7.
- Fischer T, Muhler M, Kroncke TJ, et al. Early postoperative ultrasound of kidney transplants: Evaluation of contrast medium dynamics using time-intensity curves. *Rofo* 2004;176:472–477.
- Kay DH, Mazonakis M, Geddes C, et al. Ultrasonic microbubble contrast agents and the transplant kidney. *Clin Radiol* 2009;64:1081–1087.
- Ma F, Cang YQ, Zhao BZ, et al. Contrast-enhanced ultrasound with SonoVue could accurately assess the renal microvascular perfusion in diabetic kidney damage. *Nephrol Dial Transpl* 2012;27:2891–2898.
- Tsuruoka K, Yasuda T, Koitabashi K, et al. Evaluation of renal microcirculation by contrast-enhanced ultrasound with sonazoid (TM) as a contrast agent. *Int Heart J* 2010;51:176–182.
- Dong Y, Wang WP, Cao JY, et al. Quantitative evaluation of contrast-enhanced ultrasonography in the diagnosis of chronic ischemic renal disease in a dog model. *PLoS ONE* 2013;8:e70377.
- Haers H, Daminet S, Smets PMY, et al. Use of quantitative contrast-enhanced ultrasonography to detect diffuse renal changes in Beagles with iatrogenic hypercortisolism. *Am J Vet Res* 2013;74:70–77.
- Stock E, Vanderperren K, Bosmans T, et al. Evaluation of feline renal perfusion with contrast-enhanced ultrasonography and scintigraphy. *PLoS ONE* 2016;11:e0164488.
- Paepe D, Verjans G, Duchateau L, et al. Routine health screening: Findings in apparently healthy middle-aged and old cats. *J Feline Med Surg* 2013;15:8–19.
- Brown S, Atkins C, Bagley R, et al. Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *J Vet Intern Med* 2007;21:542–558.
- Paepe D, Lefebvre HP, Concordet D, et al. Simplified methods for estimating glomerular filtration rate in cats and for detection of cats with low or borderline glomerular filtration rate. *J Feline Med Surg* 2015;17:889–900.
- Peterson ME, Becker DV. Radioiodine treatment of 524 cats with hyperthyroidism. *J Am Vet Med Assoc* 1995;207:1422–1428.
- Stock E, Vanderperren K, Haers H, et al. Quantitative differences between the first and second injection of contrast agent in contrast-enhanced ultrasonography of feline kidneys and spleen. *Ultrasound Med Biol* 2017;43:500–504.
- Debruyne K, Haers H, Combes A, et al. Ultrasonography of the feline kidney. Technique, anatomy and changes associated with disease. *J Feline Med Surg* 2012;14:794–803.
- Adams WH, Daniel GB, Legendre AM, et al. Changes in renal function in cats following treatment of hyperthyroidism using 131I. *Vet Radiol Ultrasoun* 1997;38:231–238.
- Becker TJ, Graves TK, Kruger JM, et al. Effects of methimazole on renal function in cats with hyperthyroidism. *J Am Anim Hosp Assoc* 2000;36:215–223.
- Graves TK, Olivier NB, Nachreiner RF, et al. Changes in renal function associated with treatment of hyperthyroidism in cats. *Am J Vet Res* 1994;55:1745–1749.
- Riensch MR, Graves TK, Schaeffer DJ. An investigation of predictors of renal insufficiency following treatment of hyperthyroidism in cats. *J Feline Med Surg* 2008;10:160–166.
- Vaske HH, Schermerhorn T, Grauer GF. Effects of feline hyperthyroidism on kidney function: A review. *J Feline Med Surg* 2015;18:55–58.
- Adams WH, Daniel GB, Legendre AM. Investigation of the effects of hyperthyroidism on renal function in the cat. *Can J Vet Res* 1997;61:53–56.
- Vinke EJ. Development of a contrast enhanced ultrasound technique for the measurement of cerebral blood flow in patients with acute brain injury at the intensive care unit (Thesis). In: Science and technology. The Netherlands University of Twente; 2015.
- Gauthier TP, Averkiou MA, Leen EL. Perfusion quantification using dynamic contrast-enhanced ultrasound: The impact of dynamic range and gain on time-intensity curves. *Ultrasonics* 2011;51:102–106.
- Tang MX, Mulvana H, Gauthier T, et al. Quantitative contrast-enhanced ultrasound imaging: A review of sources of variability. *Interface Focus* 2011;1:520–539.
- Hyvelin JM, Tardy I, Arbogast C, et al. Use of ultrasound contrast agent microbubbles in preclinical research recommendations for small animal imaging. *Invest Radiol* 2013;48:570–583.
- Volckaert V, Vandermeulen E, Dobbeleir A, et al. Effect of thyroid volume on radioiodine therapy outcome in hyperthyroid cats. *J Feline Med Surg* 2016;18:144–149.
- Williams TL, Elliott J, Syme HM. Association of iatrogenic hypothyroidism with azotemia and reduced survival time in cats treated for hyperthyroidism. *J Vet Intern Med* 2010;24:1086–1092.
- Stock E, Vanderperren K, Van der Vekens E, et al. The effect of anesthesia with propofol and sedation with butorphanol on quantitative contrast-enhanced ultrasonography of the healthy feline kidney. *Vet J* 2014;202:637–639.