



Relationship between indirect blood pressure and various stages of chronic kidney disease in cats

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ABSTRACT. Chronic kidney disease (CKD) is a common cause of secondary systemic hypertension in cats. We investigated the relationship between indirect blood pressure and the prevalence of systemic hypertension in various CKD stages in cats. Client-owned cats (24 control cats and 77 cats with CKD) were included. Biochemical examinations of plasma were conducted by a commercial laboratory. Diseased cats were divided into two groups based on the International Renal Interest Society (IRIS) guidelines (II and III–IV). Indirect blood pressure was measured using an oscillometric technique. Severe hypertension was diagnosed if systolic blood pressure (SBP) was ≥ 180 mmHg. Indirect blood pressures were significantly higher in IRIS stage III–IV than in the control cats. Of 77 cats with CKD, 25 (32.5%) had severe hypertension. The frequency of severe hypertension increased with an increase in IRIS stage; 0% in the controls, 27.6% in the IRIS stage II, and 47.4% in the IRIS stage III–IV, respectively. The indirect SBP was weakly correlated with urea nitrogen ($r=0.27$) and creatinine ($r=0.23$) concentrations in plasma. Binary logistic regression analysis showed that if plasma creatinine concentration is >3.7 mg/dl, cats with CKD had an increased risk for developing severe hypertension ($P<0.001$). Our results suggest that indirect blood pressure was correlated with the severity of CKD, and the prevalence of severe hypertension increased in cats with severe CKD. The risk of severe hypertension may be high in cats with severe CKD.

KEY WORDS: blood pressure, cat, chronic kidney disease, hypertension, oscillometry

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Several methods of indirect blood pressure measurement are utilized, including Doppler, oscillometric and photoplethysmographic techniques. Of these, oscillometric technique is widely used in clinical settings because they can be easily measured. Some clinical studies have shown that oscillometric technique provide diagnostic information related to systemic hypertension in cats [3, 6, 28]. If feline systolic blood pressure (SBP) exceeds 180 mmHg, it suggests an increasing risk for

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blindness and kidney injury, which is called target organ damage (TOD) [4, 25].

Feline systemic hypertension has been recognised in association with a variety of diseases, and is categorised into primary systemic hypertension, secondary systemic hypertension (i.e., chronic kidney disease [CKD]), or a measurement artifact [4, 18, 23, 24]. Because a high prevalence of CKD has been reported in hypertensive cats [15, 28, 30, 31], CKD is considered a predominant cause of secondary systemic hypertension. Several mechanisms may increase SBP in the pathophysiology of CKD in humans [8, 13, 14] and cats [17, 18]. In particular, a low glomerular filtration rate is associated with activation of the renin-angiotensin-aldosterone system in a renal failure model of cats, which may contribute to the moderately increased SBP [5, 25].

The International Renal Interest Society (IRIS) recommends classifying CKD severity based on creatinine concentrations in serum or plasma samples [16]. For example, IRIS stage II is diagnosed if creatinine concentrations are ≥ 1.6 mg/ml. Although hypertension may be present at any stage of CKD [32], the change in blood pressure in conjunction with CKD severity in cats remains unclear. We examined changes in blood pressure and the prevalence of systemic hypertension in various CKD stages in cats, and evaluated risk for the occurrence of severe hypertension.

MATERIALS AND METHODS

In this prospective, multi-centre study, 101 client-owned cats were examined between July 2014 and March 2017. The study populations of all cats consisted of mean age 12.6 years old and mean body weight 4.3 kg. Owners provided informed consent before their cats participated in the study. All cats underwent a physical examination, indirect blood pressure measurements, echocardiography, and a blood sampling, all of which were performed without sedation in a quiet examination room.

Cats

The cats were divided into two groups: controls ($n=24$) and cats with CKD ($n=77$). Because many older cats can have CKD, cats that were ≥ 5 years old were enrolled in this study. Control cats were determined to be healthy based on medical history, physical examinations, and results of biochemistry and echocardiography analyses. Creatinine concentrations were within the reference range (<1.6 mg/dl) and no clinical signs such as polyuria or polydipsia were observed. Cats with a creatinine concentration above the reference range (≥ 1.6 mg/dl) were enrolled as the CKD group. Diseased cats were further divided into two groups based on IRIS guidelines [16]: stage II (creatinine concentration 1.6–2.8 mg/dl, $n=58$) and stage III–IV (>2.9 mg/dl, $n=19$). Because the number of cats in the stage IV was relatively small ($n=3$), stage IV was combined with stage III for statistical analyses. Cats treated with fluid therapy and renal diet for CKD was included for practical reasons.

Cats with acute systemic inflammation, hyperthyroidism, cancer, liver disease, congestive heart failure, arterial thromboembolism, or urinary tract obstruction were excluded, as were cats treated with angiotensin enzyme inhibitor, angiotensin receptor blocker, glucocorticoids, nonsteroidal anti-inflammatory drugs, or antihypertensive medications at the time of the examination.

Echocardiography

Transthoracic echocardiography was performed using an ultrasonographic unit with a 7.5–12 MHz probe by experienced echocardiographers. The left atrium to aorta (LA/Ao) ratio was determined and B-mode or M-mode echocardiography was performed from the right parasternal short axis view, and the end-diastolic interventricular septum, left ventricular internal dimension, and left ventricular posterior wall were calculated. In the left parasternal long axis view, pulsed Doppler echocardiography was used to measure the transmitral flow velocity with the sample volume positioned at the tip of the mitral valve leaflets. The mitral early diastolic flow (E wave) and late diastolic flow velocities were measured. Because 61 cats (60.4%) had tachycardia and fused waves were found, the ratio of the E wave to late diastolic flow was not calculated.

Complete blood count and biochemistry

Blood samples were collected into heparinised and plain tubes, and the samples were centrifuged at 3,000 rpm (4°C) for 10 min. Biochemical examinations were conducted by a commercial laboratory (FUJIFILM Monolith, Co., Ltd., Tokyo, Japan). Thyroxine concentrations in serum were measured with an autoanalyser (FUJIFILM Monolith). In addition, blood samples were collected into tubes containing ethylenediaminetetraacetic acid for CBC. Complete blood count was performed with an automated hematology analyzer. Cats were considered to have CKD if plasma creatinine concentration was ≥ 1.6 mg/dl, to have hyperthyroidism if serum thyroxine concentration was ≥ 4.0 μ g/dl, and to have diabetes mellitus if plasma glucose concentration was ≥ 280 mg/dl.

Oscillometric blood pressure measurements

Indirect blood pressure was recorded using a noninvasive oscillometric device without sedation in a quiet examination room. All cats were allowed a minimum 5 min period of acclimation before blood pressure measurements were made. An appropriately sized cuff (inflatable bladder width approximately 0.3–0.4 times the circumference of the measurement site) was applied. Cats were minimally restrained and held in the sternal recumbency position. The cuff was placed directly around the forelimb, thus minimising the vertical distance between the cuff site and the heart. A series of five or more readings were obtained from each cat at each measurement time. The mean of the series was calculated. Measurements were performed as the initial examination. If SBP exceeded 180 mmHg, a second measurement was made after a 30–60 min period of acclimatisation to the environment. Cats were classified based on the TOD risk category provided by the American College of Veterinary Internal Medicine guidelines [4]:

Table 1. Comparison of physical examination and echocardiography among the groups

	Controls	Stage II	Stage III–IV
Male (intact/neutered)	2/9	11/21	1/9
Female (intact/neutered)	5/8	6/20	4/5
Age (Y)	12.3 (10.2–14.9)	12.6 (9.6–15.6)	14.0 (11.4–17.0)
Body weight (kg)	4.2 (3.5–5.1)	4.1 (3.2–5.6)	3.8 (2.9–4.4)
Echocardiography			
Heart rate (bpm)	176 (160–199)	182 (168–210)	180 (163–190)
IVSd (mm)	4.6 (3.6–5.3)	4.6 (4.0–5.4)	4.3 (3.6–5.9)
LVIDd (mm)	14.0 (12.5–16.2)	13.7 (12.3–15.4)	13.8 (12.4–15.0)
LVPWd (mm)	4.7 (4.3–5.4)	5.1 (4.1–5.7)	4.7 (4.2–5.8)
LA/Ao ratio	1.3 (1.2–1.4)	1.3 (1.2–1.5)	1.3 (1.2–1.5)
E wave (cm/sec)	62 (48–79)	59 (49–75)	70 (51–81)

E wave, the mitral early diastolic flow velocity; IVSd, end-diastolic interventricular septum; LA/Ao ratio, the left atrium to aorta ratio; LVIDd, end-diastolic left ventricular internal dimension; LVPWd, end-diastolic left ventricular posterior wall.

Table 2. Comparison of complete blood count and biochemical analyses among the groups

	Controls	Stage II	Stage III–IV
White blood cell ($10^2/\mu\text{l}$)	90 (55–118)	101 (69–151)	113 (90–137)
Hematocrit (%)	43 (39–46)	40 (34–43.6)	33.5 (27.6–38.7) ^{b,c)}
Platelet ($10^4/\mu\text{l}$)	22.6 (15.0–30)	27.7 (21.4–32.3)	31.3 (27.5–38.7)
Glucose (mg/dl)	124 (103–158)	122 (106–136)	127 (105–151)
Urea nitrogen (mg/dl)	27 (23–29)	34 (27–40) ^{a)}	57 (50–77) ^{b,d)}
Creatinine (mg/dl)	1.4 (1.3–1.5)	2.0 (1.8–2.4) ^{b)}	3.6 (3.4–4.3) ^{b,d)}
Sodium ($\mu\text{Eq/l}$)	154 (151–156)	154 (152–157)	156 (153–157)
Potassium ($\mu\text{Eq/l}$)	3.9 (3.5–4.1)	4.2 (3.8–4.5)	3.9 (3.6–4.3)
Chloride ($\mu\text{Eq/l}$)	119 (115–121)	118 (117–123)	119 (116–122)
Thyroxine ($\mu\text{g/dl}$)	1.8 (1.5–2.0)	1.9 (1.5–2.5)	1.5 (1.2–1.9) ^{c)}

a) $P < 0.05$ vs. controls, b) $P < 0.001$ vs. controls, c) $P < 0.05$ vs. Stage II, d) $P < 0.001$ vs. Stage II.

category I (SBP < 150 mmHg), category II (150–159 mmHg), category III (160–179 mmHg) and category IV (≥ 180 mmHg). Cats classified as category IV were considered to have severe hypertension.

Statistical analysis

All data are presented as medians (interquartile ranges [IQRs]). The Kruskal-Wallis test was used to compare the three groups. Post-hoc analyses were performed with the Dunn's test. Univariate regression analyses were used to evaluate the correlation between SBP and other variables. A stepwise regression analysis was used to determine the indirect SBP that correlated best with the individual variables. A value of $F > 2.0$ was considered statistically significant. χ^2 test was used to assess whether cats with IRIS stage III–IV were more likely to develop the severe hypertension. Binary logistic regression analysis was further performed to investigate the relationship between the severe hypertension and plasma creatinine concentrations. Odds ratio is given as 2-tailed with 95% confidence interval. A P -value < 0.05 was considered significant.

RESULTS

The study population of 101 cats consisted of 77 domestic short hairs, 10 American short hairs, 3 Scottish folds, 3 Maine coons, 3 Persians, 2 Abyssinians, and 3 other breeds. There were 11 male and 13 female control cats, ranging in age from 7.0 to 18.0 years old and weighing 2.9 to 7.6 kg, and 42 male and 35 female CKD cats, ranging in age from 5.0 to 22.0 years and weighing 1.9 to 8.8 kg. In CKD cats, 70 cats have no history of treatment and 7 cats had received previous treatment for CKD; fluid therapy ($n=7$) and renal diet ($n=2$). Ocular fundus abnormalities, i.e. mydriasis, retinal detachment, fundus hemorrhage, or retinal degeneration, were observed in 9 of 58 cats in Stage II and 4 of 19 cats in Stage III–IV.

No significant differences in age, body weight, and echocardiographic variables were found among the groups (Table 1). The results of complete blood count and biochemistry are presented in Table 2. The hematocrit values were significantly lower in the IRIS stage III–IV group than in the controls and stage II. Concentrations of urea nitrogen and creatinine increased significantly with IRIS stage. Finally, thyroxine concentrations were slightly but significantly lower in the IRIS stage III–IV group than in the stage II.

Indirect blood pressure increased concomitantly with the increase in IRIS stage (Fig. 1). Systolic and mean blood pressures were

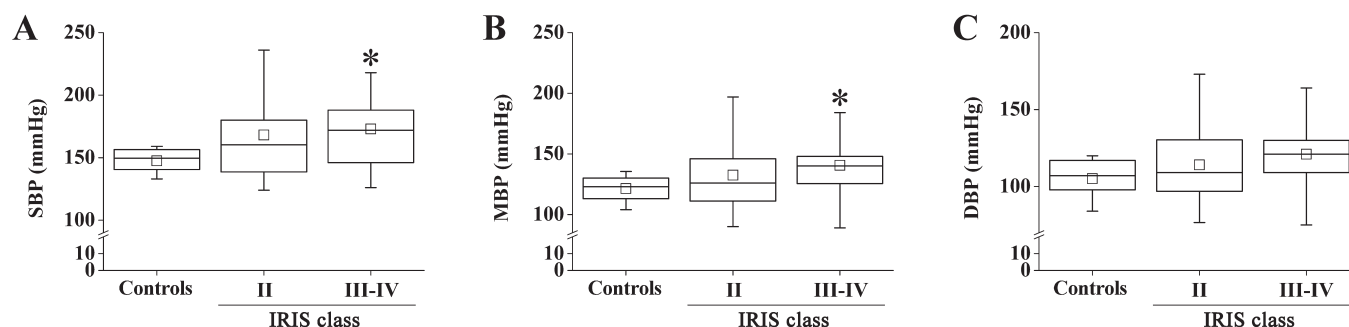


Fig. 1. Systolic, mean and diastolic blood pressure in cats with chronic kidney disease according to the International Renal Interest Society classification. The median SBP was 150 (IQR, 141–156) mmHg in the controls, 160 (139–180) mmHg in IRIS stage II and 172 (152–187) mmHg in IRIS stage III–IV. Median MBP was 123 (114–130) mmHg, 126 (111–145) mmHg, and 140 (127–147) mmHg. Median DBP was 107 (98–117) mmHg, 107 (95–123) mmHg and 121 (110–130) mmHg. DBP, diastolic blood pressure; IRIS, International Renal Interest Society; MBP, mean blood pressure; SBP, systolic blood pressure. * $P < 0.05$ vs. controls.

Table 3. Results of single regression analyses between systolic blood pressure and each variable

	<i>r</i>	<i>r</i> ²	<i>P</i> value
Age	0.35	0.12	<0.001
Body weight	−0.25	0.06	0.013
Heart rate	0.11	0.01	0.26
IVSd	0.11	0.01	0.29
LVIDd	−0.03	0.00	0.79
LVPWd	0.06	0.00	0.56
LA/Ao ratio	0.04	0.00	0.68
E wave	0.14	0.02	0.16
Glucose	−0.01	0.00	0.90
Urea nitrogen	0.27	0.07	0.006
Creatinine	0.23	0.05	0.020
Sodium	0.08	0.01	0.44
Potassium	−0.34	0.12	<0.001
Chloride	−0.02	0.00	0.82
Thyroxine	0.16	0.02	0.12

E wave, the mitral early diastolic flow velocity; IVSd, end-diastolic interventricular septum; LA/Ao ratio, the left atrium to aorta ratio; LVIDd, end-diastolic left ventricular internal dimension; LVPWd, end-diastolic left ventricular posterior wall.

Table 4. Distribution of the target organ damage risk category in cats with chronic kidney disease according to the International Renal Interest Society classification

Number (%)	Controls	IRIS stage	
		II	III–IV
TOD risk category I	12 (50.0)	20 (34.5)	5 (26.3)
TOD risk category II	10 (41.7)	8 (13.8)	2 (10.5)
TOD risk category III	2 (8.3)	14 (24.1)	3 (15.8)
TOD risk category IV	0 (0)	16 (27.6)	9 (47.4) ^{a)}

IRIS, International Renal Interest Society; TOD, target organ damage. a) $P < 0.01$ vs. controls and Stage II. Statistical differences were calculated with chi-squared test.

significantly higher in IRIS stage III–IV than in the controls. SBP was weakly correlated with age and body weight, and plasma concentrations of urea nitrogen, creatinine, and potassium (Table 3). Stepwise regression analyses showed that plasma potassium and creatinine levels ($F=8.9$ and 5.0), age ($F=5.9$), serum thyroxine level ($F=3.5$) and heart rate ($F=3.4$) predicted the indirect SBP ($r=0.60$, $r^2=0.36$, $P < 0.001$). Of the 77 cats with CKD, 25 (32.5%) were in TOD risk category I, 10 (13.0%) were in category II, 17 (22.1%) were in category III, and 25 (32.5%) were in category IV, respectively. The prevalence of TOD risk category IV, i.e. severe hypertension, in the IRIS stage III–IV was significantly different among groups ($\chi^2=13.4$, $P < 0.01$); 0% (0/24 cats) in the controls, 27.6% (16/58 cats) in the IRIS stage II and 47.4% (9/19 cats) in the stage III–IV, respectively (Table 4). Furthermore, binary logistic regression analysis showed that if plasma creatinine concentration is >3.7 mg/dl, cats with CKD had an increased risk for developing severe hypertension (odds ratio; 27.0, 95% confidence interval; 1.42–4.16, $P < 0.001$).

DISCUSSION

Renal function is thought to be a predominant factor regulating SBP in humans and animals. Spontaneous feline CKD can cause an increase in SBP [17, 21, 26, 32]. For example, a significant increase in SBP has been reported in cats with CKD (146.6 ± 25.4 mmHg) compared to normal cats (118.4 ± 10.6 mmHg) [21]. However, some studies included cats with hyperthyroidism [17, 32], or did not check thyroxine concentrations [26]. Furthermore, all studies to date have compared the SBP between CKD cats and normal cats, and the severity of CKD has varied. Thus, the detailed relationship between CKD severity and SBP remains unclear. A

novel finding of our study is that indirect blood pressures were significantly higher in severe CKD than in the controls.

In addition, renal insufficiency in cats is associated with a high prevalence of systemic hypertension [1, 11, 19, 32]. The prevalence of systemic hypertension in cats with mild to severe spontaneous CKD has been reported to range from 20 to 70% [21, 24, 32]. This large variation may reflect the different populations, i.e., CKD severity, of cats studied and different criteria for defining hypertension. In our study, SBP was classified based on the American College of Veterinary Internal Medicine guidelines, and this is the first study to report the prevalence of systemic hypertension based on severity of CKD in cats. Severe systemic hypertension was diagnosed in 32.5% of cats with CKD, and the prevalence rates of severe hypertension in cats with the IRIS stage III–IV was significantly higher than in the other groups. Furthermore, if plasma creatinine concentrations is >3.7 mg/dl, cats with CKD had an increased risk for developing severe hypertension. Taken together, the severity of CKD is associated with the indirect blood pressures, and severe CKD may have a risk of developing severe hypertension in cats.

Increased creatinine concentrations are associated with the development of systemic hypertension, as creatinine concentration reflects renal function [5, 25]. A recent study showed that creatinine concentration is the only independent risk factor for a cat becoming hypertension in CKD cats [1]. Our study also showed that indirect SBP was significantly but weakly correlated with urea nitrogen and creatinine concentrations. By contrast, no significant correlation has been reported between creatinine concentrations and SBP in humans [27] and cats [21] with CKD. Several confounding factors make it difficult to understand the relationship between creatinine concentrations and blood pressure. For example, SBP may decrease in cats with azotemia because of dehydration, and creatinine concentrations are also influenced by muscle mass. Therefore, there are some limitations when predicting SBP based on creatinine concentrations.

In addition to creatinine, univariate and stepwise regression analyses showed that age and plasma potassium concentration were associated with the indirect SBP in cats with CKD. Because spontaneous CKD is a progressive disease that potentially alters kidney function and structure over months or years, there are many elderly cats with severe CKD. Indeed, the cats with CKD had higher blood pressure readings than did the normal cats, partly because they were older [3]. Additionally, a longitudinal study demonstrated that blood pressure slightly, but significantly, increases with age (0.4 mmHg/100 days) in healthy cats [1]. These results indicate that age is a confounding factor for blood pressure increases in elderly cats with CKD. Furthermore, a previous study showed that cats with CKD and hypertension had a lower plasma potassium concentration than normotensive cats with CKD [32]. Hypokalemia is a relatively common complication in humans and cats with CKD; its prevalence is approximately 20–30% [10, 12]. In humans, hypokalemia is associated with an increase in blood pressure, and it seems to have a significant role in the regulation of blood pressure [20, 22]. However, an association between hypokalemia and hypertension has not been clarified in cats. Since CKD and these factors may interact with blood pressure in a complex manner, a definitive conclusion regarding the cause of hypertension cannot be made in our study.

In earlier studies, the accuracy of the oscillometric and Doppler techniques has been validated in cats [2, 7]. Compared with the oscillometric technique, the Doppler technique had higher correlation with direct SBP measures [2]. Similarly, the Doppler technique showed good agreement, i.e., mean error values of less than 10mmHg, whereas the oscillometric technique showed the less agreement [2]. In contrast, Caulkett *et al.* has reported that oscillometric technique provided the most accurate prediction of direct SBP (bias \pm precision; -15.9 ± 8.1 mmHg) but Doppler technique was relatively inaccurate (-25 ± 7.4 mmHg) [7]. Therefore, it is necessary to note that different measurement technique may affect the diagnostic accuracy of systemic hypertension in cats.

The present study has several limitations. First, because the autonomic nervous system (*i.e.*, stress, excitement, or fear) clearly affects SBP, cats with serious progressive lesions should be re-evaluated for blood pressure within 1–2 weeks [4]. It was difficult to re-evaluate SBP in our study, so we cannot exclude white-coat hypertension. Second, we measured plasma creatinine levels to diagnose CKD, but a diagnosis of CKD should be based on an analysis of urine specific gravity and ultrasound examination of the kidneys and urinary tract. We cannot exclude the possibility that cats in IRIS stage I were present in the control group. Third, because there were only three cats in IRIS stage IV and cats with stage I were not classified in our study, we cannot provide detailed information regarding the link between IRIS stage and changes in SBP. Finally, hypertension is both a cause and a consequence of CKD in humans [9]. Chronically high SBP can damage the kidney in humans, and has been determined to be a significant risk factor for the development of end-stage renal disease [29, 33, 34]. Further studies are required to understand whether the presence of hypertension initiates renal damage in cats.

In conclusion, this is the first study showing that the relationship between severity of CKD and indirect blood pressure in cats. Our results indicate that severe CKD may contribute to the increase in indirect blood pressure in cats. Furthermore, cats with severe CKD may have a risk of developing severe hypertension. Additional studies are required to clarify the relationship between each IRIS stage and indirect blood pressure in cats with CKD.

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