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TITLE: Systemic hypertension in cats with acute kidney injury
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Abstract

Objective: To describe the prevalence of systemic hypertension in cats with community acquired acute kidney injury (AKI) and investigate its relationship with disease severity.

Methods: Retrospective study of cats presenting to the Queen Mother Hospital for Animals, Royal Veterinary College with AKI between 2007 and 2015. Systolic blood pressure (SBP) was measured using Doppler sphygmomanometry and systemic hypertension was defined as a SBP ≥150mmHg. Median SBP measurement (on admission and during hospitalisation), IRIS (International Renal Interest Society) grade of AKI, serum creatinine on admission, the presence of anuria or oliguria, length of hospitalisation, survival to discharge and 6-month survival were all recorded.

Results: Forty-six cats were eligible for inclusion. The prevalence of systemic hypertension on admission was 48.8% (21/43) and this was severe (≥180mmHg) in 18.6% (8/43) of cases. During the whole hospitalisation period, systemic hypertension was detected in 27/46 (58.7%) cases and severe in 28.2% (13/46) cases. Systemic hypertension did not appear to be statistically associated with grade of kidney injury, serum creatinine on presentation, oliguria or anuria.

Clinical significance: Systemic hypertension is common in cats with acute kidney injury but does not appear to be associated with its severity.

Keywords: Feline, hypertension, kidney, survival, IRIS

Journal of Small Animal Practice
Introduction

Acute kidney injury (AKI) is defined as an acute and abrupt decrease in kidney function resulting in abnormalities in glomerular filtration rate, tubular function, and urine production (Hoste & Kellum 2007). AKI can be graded to encompass a continuum of functional and parenchymal damage from its least severe Grade I, a progressive increase in serum creatinine or documented oliguria over a six-hour period, to its most severe manifestation Grade V, in which renal replacement therapy may be indicated (IRIS 2013).

Progressive increases in serum creatinine have been shown to be predictive of mortality in man, dogs, and cats (Harrison et al. 2012, Hoste et al. 2006, Uchino et al. 2010). For those patients that survive AKI, reversibility of kidney injury is variable and many patients ultimately develop chronic kidney disease (CKD; Basile 2001, Chertow et al. 2006).

Systemic hypertension (SH) is a potentially serious complication of AKI in dogs and cats (Acierno & Labato 2005, Monaghan et al. 2012). The International Renal Interest Society (2015) defines systolic blood pressure (SBP) in the following categories; patients with a SBP <150 mmHg are considered normotensive, SBP of 150 to 159 mmHg are considered borderline hypertensive with a low risk of target organ damage (TOD), patients with SBP ≥160 to 179 mmHg are considered hypertensive with moderate risk of TOD and patients with SBP ≥180 mmHg have severe hypertension with high risk of TOD (IRIS 2015). The most common pathological changes reported in hypertensive cats are hypertensive choroidopathy, which can result in blindness, and hypertensive cardiac hypertrophy, which can result in a cardiac murmur or gallop rhythm (Maggio et al. 2000, Chetboul et al. 2003). A less common but severe complication of SH is hypertensive encephalopathy resulting in obtundation and seizures (Chetboul et al. 2003, Kletzmayr et al. 2003). The kidney itself has been reported to be a target organ for hypertensive injury and hypertension has been associated with progression of kidney disease in humans and dogs (Klag et al. 1996, Jacob et al. 2003, Ravera et al. 2006).

SH has been documented in cats that have CKD (Syme et al. 2002) and has been described in dogs with AKI (Geigy et al. 2011). However, the prevalence of SH in feline AKI patients is currently unknown. The aims of this retrospective study were to describe the prevalence of SH in cats with AKI and to describe its relationship with disease severity and outcome.
Materials and Methods

The study was approved by Royal Veterinary College Clinical Research and Ethical Review Board. The study population comprised of client-owned cats diagnosed with community-acquired azotaemic AKI referred to the Queen Mother Hospital for Animals, Royal Veterinary College between 2007 and 2015. These patients were identified through a search of the hospital’s computerised clinical record system. Patients were eligible for inclusion if they fulfilled the International Renal Interest Society (IRIS) guidelines for diagnosis of Grade II AKI and above, i.e. an initial serum creatinine level ≥141 μmol/L and one or more of the following criteria: evidence of renal tubular injury on urinalysis (renal glucosuria, proteinuria with an inactive sediment, or renal casts), diagnostic imaging findings suggestive of AKI, or persistent urine output of less than 1 mL/kg/hour) (IRIS 2013).

The files of eligible patients were reviewed and the signalment, cause of AKI, medical history (including prior medications), physical examination findings (including fundic examination), SBP measurements, patient-side electrolyte, metabolite and blood gas analysis, complete blood count, biochemistry, abdominal ultrasound, urinalysis, urine output measurements, length of hospitalisation and survival to discharge were recorded when available. The use of anti-hypertensive therapy was also documented. SBP was measured indirectly using Doppler sphygmomanometry. The standard hospital protocol for SBP measurements, adapted from the American College of Veterinary Internal Medicine guidelines (Brown et al. 2007), is to record the mean of three to five consecutive readings.

SH was defined as a SBP ≥150 mmHg including cats identified as borderline hypertensive (SBP 150 to 159 mmHg), hypertensive (160 to 179 mmHg) and severely hypertensive (≥180 mmHg) according to the IRIS guidelines (IRIS 2015). Patients were included if there were two or more SBP measurements within the clinical records during the period of hospitalisation. When there was more than one SBP evaluation in the clinical record on a single day of hospitalisation, a median SBP measurement for that day of hospitalisation was used for analysis. The AKI grade was determined for each patient on admission. Patients were grouped as being oliguric or anuric based on whether furosemide was administered or they underwent continuous renal replacement therapy. Patient records were analysed...
and follow-up phone calls to primary care practices were performed to identify whether those patients
that survived to discharge were still alive at six months.

Patients were excluded if they had any history, clinicopathological data or diagnostic imaging findings
suggestive of CKD including a longer history of polyuria or polydipsia, poor body condition, non-
regenerative anaemia or imaging evidence compatible with chronic nephropathy (small irregular
kidneys and loss of corticomedullary definition). Patients were also excluded if they had concurrent
diseases that could be associated with SH (including hyperthyroidism and hyperaldosteronism) or if
they had a history of pretreatment with antihypertensive drugs such as angiotensin-converting enzyme
inhibitors, beta-blockers or calcium channel blockers.

Statistical analysis

Data were assessed for normality using a Shapiro–Wilk W test and visual inspection of histograms.
Normally distributed data were expressed as mean and standard deviation and non-normally distributed
data expressed as median and ranges. Statistical analysis was performed using an online statistical
calculator (http://www.socscistatistics.com/). Fisher's exact test was used to compare categorical data,
one-way analysis of variance for ordinal data and Pearson's correlation coefficient to assess for any
correlation between SBP and serum creatinine. The level of statistical significance was set at P<0·05.

Results

One hundred and twenty cats were presented with AKI during the investigation period. Of these, 74
were excluded: 44 had incomplete data, 29 had evidence of CKD and 1 had a previous diagnosis of
hyperthyroidism. Forty-six cats were eligible for inclusion in the study, of which 44 had multiple blood
pressure measurements on a single day and required calculation of a median blood pressure. Of these
46 cats, 13 were pedigree breeds, 27 domestic short hairs and 5 domestic long hairs and for in one the
breed was not identified. Twenty-four were female neutered, 21 were male neutered and 1 cat was male
entire. Ages ranged from 5 months to 13 years with a median of two years. All cats had received fluid
therapy before presentation. Aetiology of AKI was determined in 38 cases: non-steroidal anti-
inflammatory drugs (12/46), ureteroliths (9/46), trauma (6/46), ethylene glycol (5/46), pyelonephritis
(3/46), lily ingestion (2/46) and neoplasia (1/46). In 8 of 46 cases the cause was unknown. Of the cases with ureterolithiasis, all were considered to have bilateral ureteral obstruction on review of ultrasonographic imaging. None of the cats reported to have ureteral obstruction in this study had clinical, historical or ultrasound findings specifically supporting chronic disease before the episode of AKI.

Of the 46 cats, 43 had SBP measurements on the first day of hospitalisation. The prevalence of SH (SBP ≥150 mmHg) on day 1 of hospitalisation was 21 (48.8%) and in 8 (18.6%) cases this was severe (≥180 mmHg). Four cats normotensive on admission developed hypertension in hospital and did so within the first 48 hours. Out of the three cats that did not have a blood pressure measurement on the first day, two were reported to be hypertensive on their first measurement. The prevalence of SH over the whole hospitalisation period was 58.7% (n=27), which was classified as severe in 28.2% (n=13) of cases. The mean SBP of cats on day 1 was 146.6 ±28.25 mmHg and the mean SBP over the whole hospitalisation period, excluding cats that had been started on antihypertensive therapy, was 145.25 ±29.11 mmHg.

Three cats were started on amlodipine besylate at a dose of 0.625 mg once daily. Two cats with an initial SBP over 180 mmHg were started on amlodipine on day 1 and one cat was started on amlodipine on day 2 of hospitalisation because of evidence of hypertensive retinopathy accompanying a SBP of 160 mmHg. Of these three patients one was euthanased, one became borderline hypertensive and the other remained persistently hypertensive at follow-up.

The mean SBP of cats on day 1 was 146.6 mmHg±/−28.25 and the mean SBP over the whole hospitalisation period, excluding cats that had been started on antihypertensive therapy, was 145.25 mmHg±/−29.11.

On presentation the mean serum creatinine was 1034 ±526.99 μmol/L. Initial SBP and creatinine value on presentation were not correlated (R² = 0.069, P = 0.078). Twenty-six cats were classified as having Grade V AKI, 16 classified as Grade IV and 2 each classified as Grades III and II AKI. There was no association between SH on presentation, IRIS AKI grade and survival (Table 1). When assessing the
prevalence of SH over the whole of the hospitalisation period there was not a statistically significant
association between SH during hospitalisation, and IRIS AKI grade (Table 2).

Sixteen cats were administered furosemide, two cats had peritoneal dialysis and one cat underwent
continuous renal replacement therapy. There was no statistically significant association between the
presence of SH and the presence of oliguria or anuria (p=0.54).

Twenty-five cats were euthanased during hospitalisation of which two were borderline hypertensive,
five hypertensive and seven were severely hypertensive during hospitalisation. Twenty-one cats
survived to discharge of which three were classified as borderline hypertensive, four as hypertensive
and six as severely hypertensive during hospitalisation. Of these, one cat was discharged to be
euthanased at home and three cats were euthanased within the following six months with the remaining
cats still being alive after six months. Those cats that survived had a median hospitalisation length of
seven days, ranging from 1 to 18 days.

Of the eight patients classified as severely hypertensive on presentation, three survived and five died.
Of those cats that survived, one was persistently hypertensive at re-examination despite treatment with
amlodipine, one became non-hypertensive during hospitalisation and one had incomplete records. Of
those cats that died, two became borderline hypertensive on day 2 of hospitalisation, one of which was
given amlodipine. The other three cats were euthanased between one and four days after admission and
no follow-up SBP was recorded. Five cats developed severe SH during hospitalisation of which two
were normotensive on presentation. Of these five cats, two died and three survived. Out of the three
cats that survived two became less severely hypertensive, of which one became normotensive. The
other cat had incomplete records. The other two cats were euthanased within 12 to 48 hours of
developing severe hypertension.

Discussion

This retrospective study shows that SH, including cats with borderline hypertension, is common in cats
with AKI with a prevalence of 58.7% over the course of hospitalisation; in 28.2% of cases the
hypertension was classified as severe. SH in cats has most extensively been described in patients with
CKD where studies report a prevalence varying between 19.8% and 65% (Syme et al. 2002, Stiles et al. 1994) depending on criteria used to define hypertension. with a prevalence varying between 19.8 and 65% (Stiles et al. 1994, Syme et al. 2002) depending on criteria used to define hypertension. Previous studies of feline AKI have attempted to assess prognosis and severity indices (Lee et al. 2012, Segev et al. 2013) but have not examined the prevalence of SH in detail. Segev et al. (2013) reported a prevalence of SH (defined as SBP >150 mmHg) of 38%, but included cats with “acute-on-chronic” kidney disease. Furthermore, the frequency and technique for SBP measurement was not detailed, therefore direct comparison with the current study is not possible.

In our study 54.3% of cats were euthanased in hospital, of which 56% were classified as either borderline or severely hypertensive. SBP did not appear to be correlated with IRIS AKI grade or serum creatinine at presentation. This suggests that SH in cats with AKI is not necessarily related to severity of azotaemia and AKI grade. These findings are in line with the studies of CKD in cats in which hypertension has not been found to be associated with survival or a progressive phenotype of CKD (Syme et al. 2002, Jepson et al. 2007, Bijsmans et al. 2015). In contrast, in humans and dogs, hypertension has been associated with progression of renal disease (Klag et al. 1996, Wehner et al. 2008).

Due to the small sample size and the various confounding factors of outcome including the variable prognosis of the different causes of AKI, owner finances and other co-morbidities, the association between SH and outcome could not be reliably assessed. Failure to see evidence of an association between SH and severity of AKI in this study may have been due to using creatinine as the sole indicator of kidney function [recognised to be problematic for multiple reasons including variation in hydration status and body condition between patients (Braun et al. 2003)] or the result of a type II statistical error.

Although hypertension is common in kidney disease its pathogenesis is poorly understood. Suggested aetiologies in humans have included volume-impaired excretion of sodium, leading to volume overload, excessive activation of the renin-angiotensin-aldosterone system, stimulation of the sympathetic nervous system, reduced bioavailability of the endothelial vasodilator, nitric oxide and
increased production of the vasoconstrictor endothelin and increase in reactive oxygen species (Campese et al. 2006, Pouchelon et al. 2015). To date there have been no studies of pathogenesis of SH in AKI in cats and even in CKD the pathogenesis remains poorly explained. In this study there was no association between anuria and SH. As these are the patients that are most susceptible to volume overload it could be hypothesised that volume overload was not an important cause of hypertension in this population of cats. However, improved data in terms of clinical signs relating to volume overload such as baseline body weights and body weight changes and urine output as well as an assessment of volume status (e.g. utilising bioimpedance) would be required to better evaluate this hypothesis.

Adverse effects on the ophthalmic, cardiovascular and central nervous systems has been reported in cats with hypertension (Jepson 2011). In this study, one patient had signs consistent with hypertensive retinopathy–choroidopathy. However, this was the only patient that had written documentation of a fundic examination having been performed and so the true prevalence of ocular manifestations of SH in these AKI patients cannot be reported with confidence. Nevertheless, ophthalmic examination should be recommended for patients with AKI if there is suspicion of SH and future studies should include evaluation for hypertensive ocular damage.

There are a number of limitations to this study. First, the strict inclusion criteria, particularly the exclusion of those patients with acute on CKD reduced the sample size and overall power of the study. Important records such as fundic examination findings, baseline body weights, daily weight changes and accurate urine output measurements were lacking in some cases, preventing further assessment of fluid overload and its effect on development of SH in the hospital. Urine output measurement is required for early IRIS AKI grading and to accurately diagnose a patient as anuric or oliguric and has been shown to be a prognostic factor in AKI in humans (Behrend & Miller 1996). This study did not enrol patients with IRIS AKI Grade I, and only captured two patients with IRIS AKI Grade II reducing the data distribution and therefore making it possible that the lack of association between IRIS grade and SH results from type II statistical error. The IRIS grading system itself is a useful guide for determining severity of disease but it has not yet been validated for use in AKI.
In the current study, we attempted to exclude those patients with acute-on-chronic disease based on recorded historical, physical examination and ultrasound findings. Patients with ureteroliths, without documented historical, physical examination and ultrasonographic findings consistent with CKD were included. However, due to the pathophysiology of obstructive disease and retrospective nature of the study we cannot exclude the possibility that these patients did not have underlying subclinical CKD and therefore inadvertently included some acute-on-chronic causes of AKI.

Of particular concern in this study, is the “white coat effect,” especially in those patients with fewer blood pressure readings in their clinical records. White-coat hypertension, an increase in blood pressure as a result of adrenergic stimulation during situations of stress, anxiety or excitement, has been documented in healthy cats during simulated visits to a veterinary clinic (Belew et al. 1999). In an attempt to minimise this effect on the findings of this study, when multiple blood pressure recordings were recorded on a single day of hospitalisation a median SBP reading for that day was used for the analysis. However, in some patients only a single blood pressure reading was performed on any particular day and these patients therefore carry greater risk of inappropriate classification. Due to the retrospective nature of the study there was limited information on the circumstances surrounding blood pressure measurement and the clinician's perspective on the accuracy of the single blood pressure readings. Assessment for hypertensive retinopathy–choroidopathy in all patients would have been useful to assess for evidence of TOD as part of exclusion criteria for white-coat hypertension and, ideally, continuous blood pressure monitoring would be required to completely mitigate the white-coat effect.

In summary, this study suggests SH is common in cats with AKI. However, it does not appear to be associated with disease severity or magnitude of azotaemia. This study should be considered a preliminary study for future prospective studies assessing hypertension in AKI, its persistence during hospitalisation and the effect of antihypertensive treatment on outcome.
Conflict of interest

None of the authors of this article has a personal or financial relationship with other persons or organisations that could inappropriately influence or bias the content of the paper.

References


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Table 1: Classification of systemic hypertension at presentation and its association with Acute Kidney Injury grade and survival

<table>
<thead>
<tr>
<th>SBP at presentation (mmHg)</th>
<th>Total percentage (%)</th>
<th>Number of cats</th>
<th>Survival to discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IRIS AKI grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>150 to 159</td>
<td>6/21 (28.57%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>160 to 179</td>
<td>7/21 (33.33%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥180</td>
<td>8/21 (38.09%)</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure; IRIS: International Renal Interest Society; AKI: Acute Kidney Injury

Table 2: Association between IRIS AKI grade and presence of hypertension (defined as systolic blood pressure ≥ 150mmHg) during hospitalisation.

<table>
<thead>
<tr>
<th>IRIS AKI grade</th>
<th>Number of patients</th>
<th>Mean SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>2</td>
<td>127 ±9.89</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>193.75 ±8.84</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>148.28 ±23.92</td>
</tr>
<tr>
<td>V</td>
<td>26</td>
<td>158.48 ±28.28</td>
</tr>
</tbody>
</table>

n= 46, p = 0.056

IRIS: International Renal Interest Society; AKI: Acute Kidney Injury; SBP: Systolic blood pressure