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TITLE: Systemic hypertension (SH) is a potential complication of acute kidney injury (AKI) in dogs.

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**Abstract**

**Background:** Systemic hypertension (SH) is a potential complication of acute kidney injury (AKI) in dogs.

**Hypothesis/Objectives:** To describe the prevalence of SH and hypertensive retinopathy in dogs with AKI, to investigate the relationship between SH and severity of AKI and to assess possible factors associated with SH.

**Animals:** Fifty-two dogs with AKI.

**Methods:** Prospective observational study of dogs presenting to a tertiary referral center that fulfilled the International Renal Interest Society (IRIS) guidelines for the diagnosis of AKI. Systolic blood pressure (SBP) measurement, urine protein/creatinine ratio (UPCR), urine output, presence of hypertensive retinopathy and fluid overload (FO), survival to discharge and length of hospitalization were subsequently assessed. The prevalence of SH was calculated and the relationship between SH and recorded factors was examined using non-parametric statistics.

**Results:** The prevalence of SH (≥160 mmHg) on admission or during hospitalization was 75% (39/52) and in 56% (22/39) of cases this was severe (≥180 mmHg). Sixteen percent (7/43) of dogs had evidence of hypertensive retinopathy and 77% (24/31) dogs had UPCR >0.5. Forty-two percent (22/52) dogs had FO on admission or during hospitalization. There was no association between SH and IRIS AKI grade, oligo/anuria, survival to discharge, length of hospitalization or proteinuria. Dogs with FO on presentation were more likely to be
hypertensive at admission compared to dogs without FO (p = 0.024). Dogs that did not
survive to discharge were more likely to have FO (p = 0.007).

Conclusions and Clinical Importance: SH is common in dogs with AKI. Systemic
hypertension might be associated with FO, which itself is associated with non-survival.
Monitoring for SH and FO is therefore warranted in dogs with AKI.

Introduction

Acute kidney injury (AKI) is defined as an acute and abrupt decrease in kidney function
resulting in abnormal glomerular filtration rate, tubular function and urine production.\(^1\)
Systemic hypertension (SH) is a potential complication of renal injury with variable
occurrence in both dogs and cats with chronic kidney disease (CKD) and AKI.\(^2,3,4,5\)
Systemic hypertension (SH) can lead to target organ damage which includes hypertensive
retinopathy, hypertensive encephalopathy, left ventricular hypertrophy and progression of
kidney disease. Hypertensive retinopathy occurs in both cats and dogs with CKD and
hypertensive retinopathy and left ventricular hypertrophy occurs in dogs with glomerular
disease secondary to leishmaniasis [Quatra M, Ippolito PD, Peruccico C, et al. Prevalence of
ocular lesions in dogs with systemic hypertension and nephropathy/chronic renal failure: 82
cases (2007-2010). In:Annual Scientific Meeting of the European College of Veterinary
Ophthalmologists; May 10-13, 2018 E24].\(^3,6,7\) The cause or causes of SH in kidney disease
have yet to be fully elucidated but theories include impaired excretion of sodium and
subsequent volume overload, excessive activation of the renin-angiotensin-aldosterone
system, stimulation of the sympathetic nervous system via activation of chemosensitive
afferent fibres and increase in systemic vascular resistance secondary to endothelial
dysfunction.\textsuperscript{8,9}

In dogs with CKD there is a positive correlation between systolic blood pressure (SBP) and
degree of proteinuria and both SH and proteinuria are associated with disease progression and
reduced survival time.\textsuperscript{3,10} The prevalence of SH in CKD in various studies ranges between 9-
93\%.\textsuperscript{11} Based on retrospective studies 81-87\% of dogs with AKI have SH [Francey T,
2004;18:418].\textsuperscript{4} The literature on the effect of SH on the outcome of animals with AKI is
sparse. Glomerular filtration rate is significantly reduced in hypertensive dogs compared to
non-hypertensive dogs.\textsuperscript{12} However, in AKI in cats presence of SH has no effect on survival.\textsuperscript{5}

The primary aims of this observational study were to describe the prevalence of SH and
hypertensive retinopathy in dogs with AKI. The secondary aims were to investigate the
relationship between SH and severity of AKI and to assess possible factors associated with
SH. The hypotheses were that SH would be common in dogs with AKI, but ocular target
organ damage (TOD) would be less frequently detected. We further hypothesized that there
would be no association between SH, severity of AKI or survival to discharge.

Materials and Methods

The study was approved by the Royal Veterinary College Clinical Research Ethical
Review Board (URN 2016 1590). Dogs presenting to a university referral teaching hospital
diagnosed with community acquired AKI were prospectively recruited between July 2016
and November 2018. Dogs were eligible for inclusion if they fulfilled the International Renal Interest Society (IRIS) guidelines for the diagnosis of AKI; known access to nephrotoxins, serum creatinine increase > 0.3mg/dL over a 48 hour period or serum creatinine >1.6mg/dL with one or more of the following criteria; evidence of renal tubular injury on urine analysis (renal glucosuria with normoglycemia, proteinuria with an inactive sediment and/or urinary casts), imaging findings suggestive of AKI or oliguria (urine output <1ml/kg/hr) over 6 hours.¹³

When available clinical records of the dogs were reviewed and dogs were excluded if there was any historical physical examination findings or previous clinicopathological data suggestive of CKD, including weight loss and/or polyuria and polydipsia greater than 4 weeks in duration, and previously documented azotemia with urine specific gravity <1.030.

All dogs had renal ultrasound performed and dogs were excluded if diagnostic imaging findings were indicative of CKD. These included; small irregular kidneys and the presence of renal infarcts. Dogs were also excluded if they failed to have an initial SBP or serum creatinine concentration measurement, had a co-existing disease associated with SH (including hyperadrenocorticism, diabetes mellitus, pheochromocytoma), were on medication which could result in SH (glucocorticoids, ciclosporin, toceranib), or if they had been treated with anti-hypertensive drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers or acepromazine in the 48 hours prior to enrolment.

The grade of AKI was determined by the first serum creatinine concentration recorded from serum biochemistry (iLab 600®, Instrumentation Laboratory, Cheshire UK) when available, or bedside venous blood gas and metabolite sample (ABL90 FLEX, Radiometer UK Ltd,
The underlying cause of AKI was determined based on clinician interpretation of history and clinicopathological data including haematology (ADVIA 212Oi®, Siemens Healthcare, Surrey UK), serum biochemistry, microagglutination tests (Leptospirosis MAT®, IDEXX Laboratories, Horsham UK), infectious disease testing (SNAP® 4Dx®, IDEXX Laboratories, Horsham UK), diagnostic imaging, urinalysis, urine protein/creatinine (UPCR), urine culture and macroscopic and microscopic histopathological renal findings as appropriate.

Systolic blood pressure (SBP) was measured within 12 hours of admission and at least once daily using Doppler sphygmomanometry. A standardized protocol adapted from the ACVIM consensus guidelines was used; the dog was allowed to acclimatize for 5-10 minutes before placement of a cuff (with cuff width being 30-40% of the circumference of the limb at the cuff site) on either the forelimb or hindlimb, at the discretion of the operator. The first measurement was discarded and a total of 5-7 consistent values were taken, discarding any SBP reading >20% than the other SBP measurements. The average of these readings was recorded. Based on criteria in the ACVIM guidelines dogs were grouped based on their SBP and risk of TOD; normotensive (SBP<140mmHg), prehypertensive (SBP 140-159 mmHg), hypertensive (SBP 160-179 mmHg) and severely hypertensive (SBP ≥180 mmHg). Systemic hypertension was defined as a SBP≥ 160 mmHg. Where individual dogs had more than one series of blood pressure readings performed on a given day, a median daily SBP was used for analysis. Antihypertensive therapy was at the discretion of the attending clinician.
Fundic examination was performed once within 48 hours of admission by an American or European specialist in Ophthalmology or a supervised resident in training to assess for presence of hypertensive retinopathy.\textsuperscript{11} Pupil dilation was performed at the discretion of the ophthalmologist on a case-by-case basis. The ophthalmologists were unaware of the dog’s SBP.

Urine output (UOP) was quantified either by measuring voided urine, weighing bedding or urethral catheterization. Oliguria was defined as a urine output less than 1ml/kg/hr for > 6 hours.\textsuperscript{2} Fluid overload (FO) was diagnosed by the attending clinicians who determined this based on a daily dog assessment including monitoring for acute weight gain, serous nasal discharge, chemosis, subcutaneous edema or detection of cavitatory fluid with ultrasonography.\textsuperscript{14} Proteinuria was defined as UPCR > 0.5 with an inactive sediment.\textsuperscript{15} Hypoalbuminemia was defined as serum albumin concentration <2.6g/dL.

The IRIS grade of AKI, serum albumin concentration and UPCR on admission were recorded. SBP, UOP and evidence of FO were reviewed daily. Any change in AKI grade or SH classification during hospitalization was recorded, alongside the use of anti-hypertensive agents and any extracorporeal therapy. Hospitalization length, survival to discharge, survival at 3 months and follow up serum creatinine concentration and SBP where available were documented. The prevalence of SH and hypertensive retinopathy were calculated.

**Statistical analysis**

Data were assessed for normality using a Shapiro Wilks W test and a 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 statistical software (SPSS Statistics, Version 22.0. IBM).

Descriptive statistics were used to evaluate population characteristics. A Fisher’s exact test was used to compare categorical data including number of dogs in each SBP category, AKI grade, presence of FO, proteinuria and hypoalbuminemia, and survival. A Bonferroni correction was used when comparing multiple categories. A Spearman's rank correlation coefficient was used assess for correlation between SBP, serum creatinine concentration and hospitalization length. The level of statistical significance was set at p < .05 and adjusted as needed when using the Bonferroni correction.

**Results**

Fifty-six dogs presented with AKI between July 2016-November 2018, of which 4 were excluded; 1 with prior history of anti-hypertensive therapy and 3 with incomplete data. Fifty-two dogs were eligible for inclusion in the study. Of these dogs 49 were pure breeds; the most common pure breed was the Labrador (11/49) and 5/49 were sighthounds. Three out of fifty-two dogs were cross-breeds. Nineteen (37%) were male neutered, 18/52 (35%) female neutered, 7/52 (14%) female entire and 8/52 (15%) male entire. The median age and mean weight of dogs were 57 months (range 3-120) and 24.17kg+/−12.51 respectively. Dogs presented with a variety of causes of AKI (Table 1). Where a diagnosis was made, the most common were leptospirosis (12%, n=6), prior non-steroidal anti-inflammatory drug use (12%, n=6) and hypercalcemia (12%, n=6).
Table 1: Causes of acute kidney injury in fifty-two dogs presenting to a tertiary referral center

<table>
<thead>
<tr>
<th>Cause of AKI</th>
<th>Number of dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptospirosis</td>
<td>6</td>
</tr>
<tr>
<td>NSAID use</td>
<td>6</td>
</tr>
<tr>
<td>-NSAID and GA</td>
<td>3</td>
</tr>
<tr>
<td>-NSAID and pyelonephritis</td>
<td>2</td>
</tr>
<tr>
<td>-NSAID alone</td>
<td>1</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>6</td>
</tr>
<tr>
<td>-Hypercalcaemia</td>
<td>5</td>
</tr>
<tr>
<td>-Hypercalcaemia and pyelonephritis</td>
<td>1</td>
</tr>
<tr>
<td>CRGV</td>
<td>4</td>
</tr>
<tr>
<td>Ischemia</td>
<td>3</td>
</tr>
<tr>
<td>Leishmania</td>
<td>2</td>
</tr>
<tr>
<td>Ethylene glycol toxicity</td>
<td>2</td>
</tr>
<tr>
<td>Grape and raisin toxicity</td>
<td>3</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>2</td>
</tr>
<tr>
<td>Unspecified toxin</td>
<td>1</td>
</tr>
<tr>
<td>GA</td>
<td>1</td>
</tr>
<tr>
<td>GA and rhabdomyolysis</td>
<td>1</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis not made</td>
<td>14</td>
</tr>
</tbody>
</table>
The median SBP on admission was 160 mmHg (range 50-275 mmHg). The prevalence of SH (≥160 mmHg) on admission was 54% (28/52) and in 43% cases (12/28) this was severe (≥180 mmHg). The median peak SBP at any time point was 175 mmHg (range 90-300 mmHg). The prevalence of SH at some point during hospitalization was 75% (39/52) which was severe in 56% cases (22/39) (Table 2). Forty-three out of 52 dogs had a fundic examination during hospitalization and 21% (9/43) of these had evidence of ocular TOD. Two out of these 9 dogs, one in the normotensive category and the other in the prehypertensive, did not have a hypertensive reading at any point during their hospitalization. Fundic examination findings included retinal hemorrhage (9/9), retinal vessel tortuosity (2/9), exudative retinal detachment -complete (1/9)/multifocal (1/9) and hyphema (3/9) (Figure 1a,1b). Thirty-three percent (4/12) dogs that underwent a postmortem examination had evidence of left ventricular hypertrophy, 3 of 4 were hypertensive during hospitalization and one had retinal lesions. Twenty-five out of 39 (64%) dogs diagnosed with SH at some point during hospitalization were treated with anti-hypertensive drugs. Those hypertensive dogs who did not receive anti-hypertensive therapy had a short-lived hypertension (<48 hours) or died shortly after hypertension was diagnosed. Of the treated dogs 22/25 (88%) received amlodipine alone, 1/25 (4%) received benazepril alone and 2/25 (8%) received multiple anti-hypertensive drugs. One dog received amlodipine, hydralazine and nitroprusside and the other received amlodipine, hydralazine and telmisartan. Both of these dogs had severe refractory hypertension (>200 mmHg) and evidence of ocular TOD. The dogs given telmisartan and benazepril were categorized as AKI grade I and early grade III respectively. Choice of hypertensive therapy was based on the clinician’s discretion. The median daily dose of amlodipine was 0.19 mg/kg (range 0.05-0.45 mg/kg). This was given once a day in all dogs
Table 2: Prevalence of systemic hypertension at admission and during hospitalization in fifty-two dogs with acute kidney injury

<table>
<thead>
<tr>
<th>Blood pressure category</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission</strong></td>
<td></td>
</tr>
<tr>
<td>Normotensive (&lt;140 mmHg)</td>
<td>19.2% (10/52)</td>
</tr>
<tr>
<td>Pre-hypertensive (140-159 mmHg)</td>
<td>276.9% (14/52)</td>
</tr>
<tr>
<td>Hypertensive (160 mmHg-179 mmHg)</td>
<td>310.8% (16/52)</td>
</tr>
<tr>
<td>Severe hypertension (≥180 mmHg)</td>
<td>23.1% (12/52)</td>
</tr>
<tr>
<td><strong>During hospitalization</strong></td>
<td></td>
</tr>
<tr>
<td>Normotensive (&lt;140 mmHg)</td>
<td>109.6% (5/52)</td>
</tr>
<tr>
<td>Pre-hypertensive (140-159 mmHg)</td>
<td>15.4% (8/52)</td>
</tr>
<tr>
<td>Hypertensive (160 mmHg-179 mmHg)</td>
<td>323.7% (17/52)</td>
</tr>
<tr>
<td>Severe hypertension (≥180 mmHg)</td>
<td>42.3% (22/52)</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury  CRGV, Cutaneous and renal glomerular vasculopathy GA, General anesthesia NSAIDS, non steroidal GA, General anesthesia CRGV, Cutaneous and renal-glomerular vasculopathy
initially but was escalated to twice daily in one dog and given initially three times daily as incremental dose management in another in attempt to manage severe hypertension. Anti-hypertensive therapy was associated with a reduction in hypertension category in 14/25 (56%) of cases; 2/14 severe to normotensive, 7/14 severe to pre-hypertensive, 3/14 severe to hypertensive and 2/14 hypertensive to normotensive. Twelve of the 25 (48%) dogs given anti-hypertensive did not survive to discharge. Of the 13/25 (52%) dogs given anti-hypertensive therapy that did survive to discharge 7/13 (54%) were discharged on therapy, 4/13 (31%) had short lived hypertension in hospital and 2/13 (15%) were discharged to be euthanized.

The median serum creatinine concentration on presentation was 5.53mg/dL (range 1.39-19.56mg/dL). Five dogs out of the 52 (10%) had grade I AKI, 2/52 (4%) grade II, 17/52 (33%) grade III, 17/52 (33%) grade IV and 11/52 (21%) grade V. Fourteen dogs (28%) had an increase in AKI grade during hospitalization. There was no correlation between initial SBP and serum creatinine on presentation (r= 0.182, p= 0.20). The prevalence of SH ranged between 50-91% across AKI grades (Table 3). There was no association between the presence of SH on admission or during hospitalization and IRIS AKI grade on presentation or increase in AKI grade during hospitalization.

Twenty-nine out of 49 dogs were hypoalbuminemic (59%). The mean serum albumin concentration was 2.53g/dL +/- 0.54 (n=49). Thirty-four dogs had an UPCR measurement, of which 1/34 had gross hematuria and 2/34 had an active sediment and so these dogs were not included in further analysis. The median UPCR in the 31 remaining dogs was 1.68 (range 0.1-18). Twenty-four out of thirty-one dogs (77%) had UPCR > 0.5 of which 14/24 (58%)
Table 3: Prevalence of systemic hypertension and acute kidney injury grade on admission in fifty-two dogs with acute kidney injury

<table>
<thead>
<tr>
<th>IRIS AKI grade</th>
<th>Prevalence of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>60.0% (3/5)</td>
</tr>
<tr>
<td>II</td>
<td>50.0% (1/2)</td>
</tr>
<tr>
<td>III</td>
<td>94.1% (16/17)</td>
</tr>
<tr>
<td>IV</td>
<td>71.0% (12/17)</td>
</tr>
<tr>
<td>V</td>
<td>91.0% (10/11)</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury  IRIS, International Renal Interest Society  AKI, acute kidney injury
had a UPCR above 2. There was no association between presence elevated UPCR and hypoalbuminemia, or SH on admission or during hospitalization.

A urethral catheter was placed in 54% (28/52) dogs. When considering all methods of urine measurement the median urine output was 1.4ml/kg/hr over the entire hospital period ranging from 0-25ml/kg/hr. Forty-two percent of dogs (22/52) were reported to be oliguric (urine output <1ml/kg/hr for > 6 hours), all of which received furosemide. Seven out of twenty dogs received a single bolus dose between 0.5-2mg/kg, 2/20 dogs had a bolus between 0.5-1mg/kg prior to a continuous infusion of 0.1-2mg/kg/hr and 11/20 had a continuous infusion between 0.25- 0.8mg/kg/hr. In two dogs the bolus dose of furosemide was not recorded. There was no association between the presence of SH and the presence of oliguria or anuria (p= 0.22). Six dogs had extracorporeal therapy, 4/52 (78%) had continuous renal replacement therapy (CRRT) and 2/52 (4%) had total plasma exchange. All four dogs that underwent CRRT were hypertensive on admission.

Twelve dogs (23%) were considered to have FO on admission and 10/52 (19%) developed FO during hospitalization. Forty-two dogs (81%) received intravenous therapy prior to admission and 94% (49/52) received fluids at some point during hospitalization. In those dogs with FO on presentation, fluid therapy was administered after furosemide in 6/10 (60%), extracorporeal therapy in 2/10 (20%) and for replacement of varying insensible and sensible losses in 2/10 (20%) dogs. There was a significant association between FO on admission and SH on presentation (p= 0.024) but there was no association between SH and the development of FO in hospital.
Twenty-five (48%) dogs survived to discharge and 3 dogs (6%) were discharged home for euthanasia. Of those dogs that did not survive to discharge 22/24 (92%) were euthanized and 2/24 (8%) died. The mean length of hospitalization for the surviving dogs was 8.48 days +/- 4.13. There was no correlation between the SBP and hospitalization length for dogs that survived (rs =0.225, p=0.28). There was no association between survival to discharge and SH on admission or during hospitalization, nor was there an association between IRIS AKI grade and survival. There was an association between the presence of FO at any point during hospitalization and survival to discharge (p =0.007).

In those dogs that survived to discharge, 32.0% (8/25) were lost to follow up. Out of the remaining dogs 29% (5/17) died within 3 months. Of the five dogs that died within 3 months 2/5 were euthanized directly as a result of their AKI, 2/5 were euthanized as result of an underlying neoplastic process and 1/5 died of unrelated causes. Overall 3-month survival rate of all dogs available for follow up was 28% (12/44). The presence of SH at admission and during hospitalization was not associated with three-month survival. Five out of ten (50%) dogs that had serum creatinine measured within the 3 month follow up period after discharge had a serum creatinine above the upper limit of the laboratory defined value of >1.63mg/dL. All of these dogs were hypertensive at some point during hospitalization. Four out of five dogs who had blood pressure measurements between 2-12 week after discharge were found to be hypertensive and on therapy.

Discussion

This prospective study shows that the prevalence of SH is high in dogs with community acquired AKI and appears to increase during hospitalization; 54% of dogs were hypertensive
on presentation and 43% had severe hypertension. These values increased to 75% and 56% respectively during hospitalization. These results are similar to the currently reported SH occurrence rate of 81-87% in dogs with AKI during hospitalization. There is therefore a clear requirement for frequent blood pressure monitoring of animals hospitalised with AKI.

Hypertensive retinopathy was detected in 16% dogs in this study. This is less than reported in a study of all causes of hypertension, which report a prevalence of 62%. However, the prevalence is similar to that previously described in dogs with CKD. The low prevalence of hypertensive retinopathy could be explained by the low number of dogs presenting with severe hypertension, the low rate of repeat ophthalmological examinations, or failure to detect early retinal lesions, as pupil dilation was not performed in all dogs. Two dogs, one in the normotensive category and one in the pre-hypertensive category, also had retinopathy consistent with hypertension. One of the dogs had AKI secondary to a combination of presumed renal hypotension secondary to general anesthesia and laparoscopy, and non-steroidal anti-inflammatory drug therapy. Retinal hemorrhage occurs in humans undergoing laparoscopic surgery suspected to be secondary to increased retinal venous pressure and therefore could explain this finding. Alternatively, these findings could be explained by underestimation of the diagnosis of hypertension as a result of inherent inaccuracies of indirect measures of SBP, or could suggest that macroscopic retinal vascular changes are not sensitive indicators of early ocular TOD. Studies of early stage untreated
essential hypertension in humans failed to find a relationship between retinal microvascular changes and other validated markers of TOD such as 24-hour ambulatory blood pressure monitoring, 24-hour urine collection for microalbuminuria, echocardiography and carotid ultrasonography.18 Despite the seemingly low prevalence of hypertensive retinopathy in AKI, systemic heparinization in the presence of retinal hemorrhage could lead to severe retinal damage. An ophthalmological exam should therefore be considered in all AKI dogs prior to CRRT.

There was no association between evidence of hypertensive retinopathy and severity of SH. This might be the result of a type II error due to the low numbers of dogs with evidence of hypertensive retinopathy or the temporal relationship between detection of SH and fundic examination. Fundic examination was standardized to occur in the first 48 hours and the number of severely hypertensive dogs at admission was low. Another factor shown to affect the development of TOD in people is the variability of SBP; greater variability of SBP has been shown to associated with greater risk of TOD.19 SBP variability was not assessed in this study but is something that should be considered in future studies.

Left ventricular hypertrophy, indicative of cardiac TOD has been reported in 91% of hypertensive dogs with leishmaniasis, of which over half of the dogs had kidney disease.7 In our study 4/12 dogs that underwent a postmortem examination had evidence of left ventricular hypertrophy, of which three quarters of them were noted to be hypertensive during hospitalization and 1/4 had retinal changes. These findings suggest a degree of chronicity of the SH and therefore might indicate a failure to diagnose chronic kidney disease in this subset of dogs. However, the possibility of the AKI occurring secondary to SH cannot
be excluded. These results suggest other diagnostic tests such as echocardiography should be used alongside a fundic examination to further assess for TOD.

Proteinuria has been associated with SH and persistent proteinuria is considered a finding indicative of TOD. Studies report a positive but non-linear correlation between SBP and UPCR in dogs. Proteinuria might also be the result of primary glomerular disease. A UPCR >2 alongside hypoalbuminemia is considered consistent with glomerulonephropathy and SH has been shown to associate with glomerular disease in dogs. In our study over 75% dogs had a UPCR > 0.5 of which 58% had UPCR >2. Few previous studies have quantitatively assessed proteinuria in AKI dogs; 78% dogs with leptospirosis were reported to have an elevated UPCR and in another study of 125 dogs UPCR values between 0.09-72 were reported in dogs with AKI of all causes and the degree of proteinuria was significantly greater in non-survivors. In the current study there was no association between proteinuria and hypoalbuminemia, SH and survival to discharge. Failure to detect an association between SH and proteinuria might be the result of a type II error due to the small number of dogs with UPCR measurement or secondary to the effect of treatment; hypertensive dogs were treated at the clinician’s discretion and many had improvement in their SBP category which could have masked an association between SH and proteinuria. Alternatively, the proteinuria could have been predominantly tubular in origin rather than a result of glomerular hypertension. Future studies with renal biomarkers of glomerular and tubular injury such as fractional excretion of IgG and IgM and urine neutrophil gelatinase-associated lipocalin (NGAL) alongside trending of UPCR in dogs with AKI over time might help determine the origin of this proteinuria and could have significant consequences of the choice of anti-hypertensive therapy.
There was no association between the presence of SH and IRIS AKI grade or absolute serum creatinine concentration. This is similar to findings in cats with AKI and in dogs with cardiorenal syndrome. These findings suggest SH can occur at all grades of AKI. Interestingly, canine studies have shown a reduction in glomerular filtration rate (GFR) correlates with an increase in SBP. In an experimental canine study, hypertensive dogs had a significantly reduced GFR and increase in renal tubular lesions and fibrosis compared to normotensive dogs in the weeks to months after AKI, suggesting SH has appreciable adverse effect on kidney structure and function. In the current study SH was treated at the clinician’s discretion and hypertensive category reduced in around half of the dogs. This intervention could have masked the potential effect of SH on disease progression and outcome. Furthermore, the number of cases loss to follow up was high and follow up sampling was not standardized reducing the study’s power to detect the long-term effect of SH on kidney function. Finally, the IRIS guidelines used in this study for grading AKI are based on serum creatinine concentrations alone which is not considered an accurate indicator of GFR. Future studies should therefore consider the routine use of commercial measures of GFR at standardized follow up time points.

There was no association between SH at admission or development during hospitalization and survival nor between AKI grade and survival to discharge. The failure to detect an association between SH and survival to discharge is similar to that reported in cats with AKI. Dogs enrolled had no pre-treatment with anti-hypertensive agents and therefore we can reliably assess the effect of previously untreated SH on admission with disease severity and outcome. However, during hospitalization anti-hypertensive therapy was administered at the clinician’s discretion and in around half of treated dogs their hypertension resolved. It is therefore difficult to elucidate the effect of persistent hypertension on outcome in this study.
It is plausible that anti-hypertensive therapy masked the effect of SH on survival. The lack of association between severity of AKI and outcome is surprising and contrary to previous studies of AKI whereby increased AKI grade was associated with worsened outcome. This difference could be explained by differences in causes of AKI in our population versus others and the over-reaching effect of etiology on outcome in AKI irrespective of absolute serum creatinine concentration. The study’s small size, particularly the number of dogs in lower AKI grades, might also contribute to failure to detect an effect of AKI grade and outcome.

Of those dogs which survived and for which information was available, 50% were azotemic on one or more occasion after discharge. All of these dogs were hypertensive at some point during hospitalization. Inferences on the effect of SH on development of CKD cannot be made given the small number of dogs, but this supports the need for regular monitoring of dogs after an episode of AKI. Only five dogs had follow-up blood pressure, of which 4/5 were persistently hypertensive and on anti-hypertensive therapy. Monitoring blood pressure after discharge is particularly important considering human AKI dogs are more likely to develop hypertension during follow up.

Despite the frequent occurrence of SH in dogs with kidney disease the pathogenesis is poorly understood. Suggested etiologies include volume impaired excretion of sodium leading to volume overload, excessive activation of the renin angiotensin-aldosterone system, stimulation of the sympathetic nervous system secondary to activation of chemosensitive afferent neurons by local ischemia and inflammation, reduced bioavailability of the vasodilator nitric oxide and increased production of the vasoconstrictor endothelin. In this study the presence of SH at admission was associated with the presence of FO at admission.
suggesting a role for volume and sodium excess in the pathogenesis of hypertension in this population. It is unclear why this relationship did not persist during hospitalization but the authors hypothesize it is related to the duration of FO; during hospitalization daily frequent monitoring of weight encourages early detection of FO. This might prompt the de-escalation of fluid therapy prior to the development of clinically detectable volume overload. In human dialysis, dogs’ volume status, particularly those with FO are associated with both pre-dialysis and post-dialysis blood pressure. Blood pressure falls during hemodialysis with fluid removal and the decrease in blood pressure is greatest with larger amounts of fluid removal and with higher ultrafiltration rates. In the current study, four dogs underwent continuous renal replacement therapy as part of their management, all of which were hypertensive. SH did not resolve after therapy in any of the dogs, despite resolving their FO, suggesting this might only partly contribute to SH in AKI. Further studies of volume status in dogs with AKI and SH, using standardized measures of volume status such as bioimpedance are required. In this study the presence of FO at any point during hospitalization was also associated with a reduced survival to discharge and this is consistent with studies in critical dogs and people undergoing renal replacement therapy. This finding highlights the need for careful monitoring and judicious fluid therapy dogs with AKI.

Amlodipine at a daily dose range of 0.1-1.2mg/kg was the predominant therapy for hypertension used in this study. One dog received a dose above the recommended range of 0.1-0.5mg/kg PO similar to a previous study where doses up to 1mg/kg were required. Despite treatment, the hypertensive category only reduced in around half of the treated dogs. Failure to achieve control is likely due to failing to appropriately adjust anti-hypertensive medication in light of persistent hypertension, particularly in those dogs who had shorter survival times. Additional contributing factors include; the potential
for reduced oral bioavailability of amlodipine in critically ill dogs\textsuperscript{32} and secondary glomerular hypertension as a consequence of preferential afferent arteriole vasodilation with amlodipine therapy.\textsuperscript{11} Further studies assessing amlodipine levels, proteinuria, and continuous blood pressure measurements in critical AKI dogs are required to best determine the dose and role of the drug in these dogs.

This study had several limitations. It was conducted in a referral center and therefore the availability of complete medical records prior to referral was variable and the majority of dogs received treatment, including fluid therapy, prior to referral. The diagnosis of FO involved subjective assessment and was therefore less accurate than determining fluid balance based on calculations of fluid in and fluids out and the use of bioimpedance techniques.

AKI grade was determined based on the first recorded serum creatinine concentration and therefore the method of measurement was not standardized. This could lead to inter-individual variation in serum creatinine concentration and could affect subsequent AKI grading. Furthermore, only seven dogs with IRIS AKI grade I and II were enrolled reducing the distribution of data. Being a clinical study there was no pre-defined guidelines for management of SH, nor was there a control un-treated group of dogs. This, therefore, limits the study’s power to determine the effect of SH on AKI severity and outcome. Furthermore, there was no standardization of management of dogs once discharged and there was a high occurrence of loss to follow up of dogs that survived to discharge. This, thereby limits the assessment of the effect of SH on longterm kidney function. Further studies should focus on the efficacy of pre-defined anti-hypertensive therapy and routine follow up including serum
creatinine and other biomarkers of kidney function, urinalysis and GFR measurements to
fully assess the effect of SH and development of CKD.

Situational hypertension, an increase in blood pressure as a result of adrenergic stimulation
during situations of stress or anxiety, is difficult to control in any clinical study.\textsuperscript{11} Situational hypertension has been documented in hospitalized dogs, in particular greyhounds.\textsuperscript{31,33,34}
Furthermore, greyhounds have significantly higher SBP than other breeds.\textsuperscript{35} In this study there were 5 sighthounds and 3/5 were considered hypertensive, of which two had SBP over 180 mmHg. Although in the majority of studies the increase in blood pressure in the hospital was marginal, values up to 200 mmHg are reported and therefore the presence of situational hypertension could lead to misclassification of dogs in all hypertensive categories.\textsuperscript{35,36}
Despite hospital protocols being in place to minimise the effect of stress on the blood pressure readings and following ACVIM guidelines\textsuperscript{11} to measure blood pressure, the prevalence of SH in this study might have been increased by dogs with solely situational hypertension. Continuous blood pressure monitoring would be required to fully mediate the effect of situational hypertension.

Doppler sphygmomanometry is a recognised indirect measure of blood pressure. However, indirect blood pressure measurements have been shown to underestimate SBP in the hypertensive dog and therefore using this methodology might have underestimated the true prevalence of SH.\textsuperscript{37} The gold standard technique for measurement of blood pressure is direct arterial catheterization, but is not practical in this subset of dogs. Telemetric blood pressure measurement could be useful both during hospitalization and after discharge to reliably detect SH, TOD and the effect of treatment in dogs with AKI.\textsuperscript{38}
In summary, SH is common in dogs with AKI. However, hypertensive retinopathy appears to be uncommon. Systemic hypertension can occur at all grades of AKI and therefore SBP should be monitored in all dogs with AKI irrespective of severity. Systemic hypertension on admission does not appear to affect outcome, however, in light of the routine use of anti-hypertensives the effect of persistent SH on outcome cannot be fully elucidated from this study. The relationship between FO and SH needs to be further explored but considering FO was associated with worsened outcome measures should be taken to monitor for, and prevent FO in dogs with AKI.

References


