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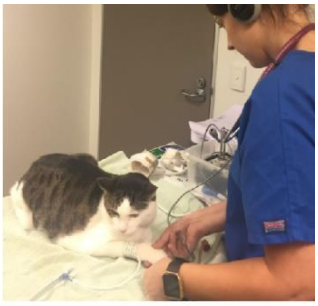
Investigating Feline Hypertension



Blood pressure measurements should be performed in a quiet location with minimal restraint

Aetiology and pathogenesis of hypertension

Systemic hypertension is a persistent increase in blood pressure (BP) that generally occurs with underlying disease in cats. Chronic kidney disease (CKD) and hyperthyroidism are most commonly associated with hypertension with 20-65% of cats with CKD and 9-23% of hyperthyroid cats reported hypertensive.
Hypertension is also seen with other diseases as detailed in the table below. Primary hypertension (idiopathic hypertension) is identified in less than 20% of hypertensive cats. This discussion will focus primarily on hypertension associated with CKD.

Possible causes of hypertension in cats	
Chronic kidney disease	Hyperthyroidism
"White coat" hypertension (false hypertension)	Primary hypertension (idiopathic hypertension)
Primary hyperaldosteronism (Conns syndrome)	Phaeochromocytoma
Chronic anaemia	Secondary to erythrocyte stimulating agents (e.g. darbepoietin) or other drugs
Hyperadrenocorticism	

Azotaemia is a risk factor for hypertension. Most hypertensive cats are azotaemic (67%) however severity of azotaemia does not predict hypertension. Often, hypertensive cats are only mildly azotaemic (e.g. creatinine <300 µmol/L), possibly because cats with more severe azotaemia are hypovolaemic (e.g. due to gastrointestinal (GI) haemorrhage) and subsequently hypotensive. The only risk factor identified for hypertension in a study of 103 CKD cats was the presence of hypokalemia.

The pathogenesis of hypertension is multifactorial, but likely involves renin-angiotensin-aldosterone system (RAAS) activation, altered sodium excretion, increased sympathetic activity, altered prostaglandin/bradykinin production, altered production or response to nitric oxide and/or other endothelium derived factors, renal secondary hyperparathyroidism (RHPTH) and arterial structural changes. Aldosterone concentration is higher in cats with CKD and hypertension.
Hypertension causes damage to the kidneys in other species and is a poor prognostic indicator in dogs with CKD. Effects in cats are not as clear. If hypertension does damage the feline kidney, ensuring control of hypertension should improve survival times, however this has not been found in cats. Although systolic BP (SBP) in cats correlates with the severity of proteinuria, and proteinuria is associated with survival, cats treated for hypertension did not demonstrate reduced survival time when compared to cats without hypertension. Despite this, the risk of damage to other body organs due to hypertension (target organ damage (TOD)) such as retinal detachment, justifies screening and treating hypertension in CKD cats.
Screening may also be considered in healthy cats to obtain baseline levels for individual patients. Routine ocular examination is also recommended for all cats over 10 years of age.

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Recommendations for monitoring of systolic blood pressure in healthy patients

Category	Frequency of SBP monitoring
Healthy adult cat (3-6 years of age)	Consider every 12 months*
Healthy senior cats (7-10 years of age)	Every 12 months
Healthy geriatric cats (>11 years of age)	At least every 6-12 months
Cats with recognised risk factors including: • CKD, hyperthyroidism (including treated cats), primary hyperaldosteronism, hyperadrenocorticism, phaechromocytoma • Drug therapy e.g. darbopoietin • Evidence of target organ damage	Measure immediately and reassess at least every 3-6 months For darbopoietin – check BP prior to every treatment

*The main purpose of monitoring in this age group is to obtain baseline measurements for the individual cat. As few cats in this age category have hypertension, caution is needed in the interpretation of elevated blood pressure measurements, especially in the absence of target organ damage or clear underlying disease. The author does not routinely measure SBP in cats under 7 years of age that do not have other co-morbid diseases.
#Table modified from ISFM Consensus Guidelines on the Management of Hypertension in cats 2017.

Clinical signs of hypertension

Clinical signs associated with hypertension occur due to damage of target organs that are particularly affected by the presence of hypertension including the:

- Brain
- Cardiovascular system
- Kidneys
- Eyes.

Unfortunately, most clinical signs associated with hypertension occur late in the course of disease once TOD is already present.

Target Organ	Suspected mechanism of damage	Clinical findings	Prevalence in all hypertensive cats*
Brain	Hypertensive encephalopathy Arteriosclerosis of cerebral blood vessels CNS oedema CNS haemorrhage	Behavioural changes Night vocalization Dementia Altered mentation Depression Ataxia Seizures Coma Focal neurological deficits Brain or spinal cord Sudden death	15%
CV	Left ventricular hypertrophy CHF (rare)	Murmur Arrhythmia Gallop Left ventricular hypertrophy Asymmetric septal hypertrophy Aortic root dilation Epistaxis	50-80%
Kidneys	Glomerular hypertrophy and sclerosis Nephrosclerosis Tubular atrophy Interstitial nephritis	Reduced USG Azotaemia Proteinuria	Unknown

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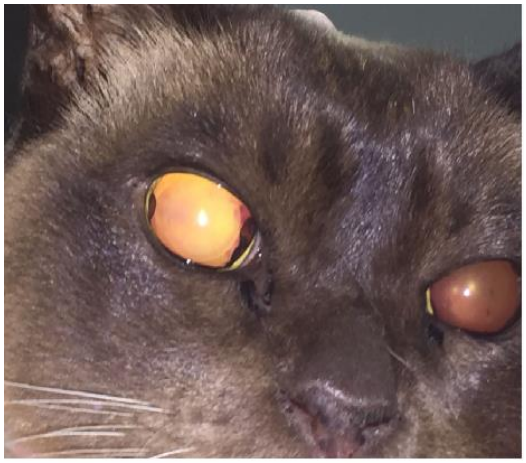
Eyes	Hypertensive retinopathy/choroidopathy Hyphaema Retinal oedema Retinal detachment Arterial vessel tortuosity Papilloedema Glaucoma Retinal degeneration	Blindness Altered behaviour Mydriasis	60-80%

CHF: Congestive heart failure; CNS: central nervous system; CV: cardiovascular; USG: urine specific gravity
* Prevalence across all causes of hypertension, not just in cats with CKD



Blindness and hyphaema are common presenting signs of hypertension in cats

Diagnosis of hypertension

Ideally, BP measurement includes both SBP and diastolic BP (DBP). Unfortunately, little information is available regarding DBP in cats and accurate measurement is difficult. Conversely, SBP measurement is easy and economical to perform. Both Doppler and oscillometric machines are available. The Doppler technique is better tolerated, and more reliable in conscious cats.

Both Doppler and Oscilomtric machines are useful for measuring blood pressure in cats

Which site is utilised for BP measurement may vary depending on the practitioner and the patient. It is likely the most appropriate site is that which the practitioner is familiar with and the cat will tolerate.
One study has suggested the coccygeal artery is better tolerated compared with radial artery assessment when using an oscillometric machine. Interestingly, SABP measurements were 8.7% higher when this site was used. A later, similar study found high individual variation in measurements utilising both coccygeal vs radial artery assessment, particularly in obese cats where it was postulated that a cone-shaped

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tail could lead to distal gaping or slipping of cylindrical cuffs and peripheral pulse pressure amplification.

Technique for SBP measurement

SBP is obtained using the following method:

1. Choose a quiet area away from other animals. Allow the cat time to acclimatise to the environment (5-10 minutes).
2. In many cats, SBP is easily measured in the consultation room with the owner present and gently restraining the cat.
3. Only very gentle restraint is required in the majority of patients.
4. Metacarpal, metatarsal and coccygeal (tail) sites maybe utilised. Clipping is rarely necessary and may further agitate the patient.
5. The cuff size should be 40% of the circumference of the site where the cuff will be placed. This is generally a 2.5cm cuff in most cats.
6. The cuff should be placed level with the heart if possible.
7. Secure the cuff in place using the Velcro tabs. Often a small amount of adhesive tape is necessary.
8. Palpate the pulse and wet the hair down over the site with alcohol.
9. Ensure the Doppler machine is switched OFF. This will prevent a large amount of static noise occurring during manipulation which elevates the BP of everyone involved. Alternatively, headphones can be used.
10. Apply a generous amount of gel to the Doppler probe.
11. Alcohol damages probes. Ensuring adequate gel is present will prevent alcohol coming into contact with the probe itself.
12. Gently place the probe over the prepared area and switch ON the Doppler. Gradually increase the volume.
13. Listen for the pulse signal, moving the probe gently in small increments until the pulse signal is clear.
14. If the pulse signal is poor or inaudible, switch off the machine, remove the probe and add more gel. If this doesn't help, choose an alternative site.
15. Once the pulse signal is clear, gently inflate the cuff using the sphygmomanometer. Inflate the cuff 10-20 mmHg beyond the point at which the pulse becomes inaudible.
16. Slowly deflate the cuff until the pulse signal returns. The SBP is the pressure at which the pulse signal first becomes audible.
17. Allow the cuff to deflate completely.
18. Discard the first measurement. Repeat steps 15-17 to obtain 5 measurements.
19. The SBP is the average of these 5 measurements.
20. The site and cuff sized used should be recorded and the same technique repeated at subsequent visits.

Interpretation of SBP results

Normal SBP reference intervals are 120-160 mmHg. SBP is also classified based on the risk of TOD as used in the IRIS staging scheme.

RISK OF HYPERTENSION-RELATED COMPLICATIONS		
Risk category	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Minimal risk (N)	<140	<95
Low risk (L)	140-159	95-99
Moderate risk (M)	160-179	100-119
High risk (H)	>180	>120

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White-coat hypertension (stressed induced hypertension) is common in cats, causing transient increases in SBP. White-coat hypertension may result in an erroneous diagnosis of hypertension and unnecessary treatment. The effect of white-coat hypertension is highly variable. SBP increases can be high in some patients (reported up to 75 mmHg). Interestingly, neither demeanour (i.e. very relaxed) nor heart rate, can predict the occurrence of white-coat hypertension. Additionally, in one study there was no effect of training (5 simulations over 5 weeks) in reducing the occurrence of white-coat hypertension.

Increased SBP is confirmed by repeat testing throughout the day. Additionally, the cat is evaluated for evidence of TOD (e.g. fundic examination and ideally echocardiography) to give additional support to the result.

If TOD is identified, hypertension is likely. If no evidence of TOD is present, SBP measurement is repeated within 1-2 weeks (or 1-2 days if SBP >200 mmHg). If results remain elevated, hypertension is likely.

Patient signalment should also be considered. Most hypertensive cats are elderly; hypertension is rarely identified in cats under 10 years of age. If hypertension is identified in a younger cat with no evidence of CKD, hyperthyroidism or TOD, white-coat hypertension is likely.

Treatment of hypertension

Management goals of hypertension are to identify and reduce TOD, reduce SBP to within reference intervals and ideally, resolve the underlying cause of the hypertension. In hypertensive CKD cats, the latter, is unlikely to be achieved. With hyperthyroidism treatment (e.g. radioactive iodine) and adrenalectomy in cats with primary hyperaldosteronism, hypertension may resolve.

When to initiate treatment?

Hypertension must be persistent prior to initiation of treatment, unless TOD is present. Antihypertensive medication is never initiated on the basis of a single elevation in SBP.

Repeat measurement recommendations to ensure persistent hypertension in cats

Risk category	SBP (mmHg)	Repeat measurement time frame to ensure persistent finding if no evidence of TOD	Treatment required?
Minimal risk (N)	<150	Not required	No treatment required
Low risk (L)	150-159	Repeat measurement in 1-3 months if underlying disease associated with hypertension (e.g. CKD) present	No treatment required unless evidence of TOD
Moderate risk (M)	160-179	Repeat measurement in 1-2 months	Treatment required if TOD evident or underlying disease (e.g. CKD, hyperthyroidism) present and elevation persistent
High risk (H)	>180	Repeat measurement in 7 days if 180-200 mmHg Repeat measurement in 1-2 days if >200 mmHg	Treatment required if TOD evident or repeat measurement persistently elevated

SBP: systolic blood pressure; TOD: target organ damage

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Dietary Sodium

Reducing dietary sodium is important in humans with hypertension, however no evidence suggests dietary sodium restriction is beneficial in hypertensive cats. Still, excessive sodium intake should be avoided. Ideally dietary salt intake should remain constant and sudden increases in sodium (e.g. high salt treats) should be avoided. Foods to avoid (that might be considered for administering medications) include condiments (e.g. tomato sauce), sandwich meats and most commercial pet treats. Alternatives could include lean cooked meats (e.g. chicken, turkey, beef or fish), cooked eggs, or homemade chicken or fish broth.

Calcium channel blockers (CCB)

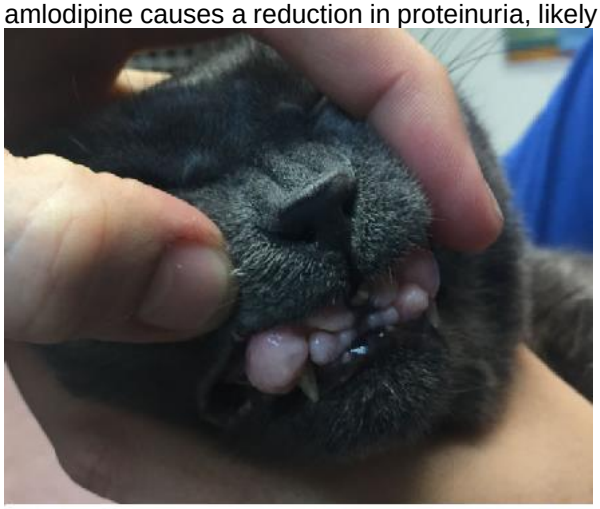
Amlodipine, is effective in reducing hypertension, proteinuria, TOD risk and improving quality of life in cats. Amlodipine acts on L-type voltage operated channels on arterial smooth muscle causing vasodilation and BP reduction. Few side effects, rapid onset, low cost and easy administration make this the first choice for hypertension control. Amlodipine is highly efficacious and typically reduces SBP by 30-55 mmHg. It is useful as a sole agent and well tolerated by most cats. Crushing the tablet doesn't alter bioavailability in humans. Transdermal amlodipine is available, however bioavailability is reduced and unpredictable.

Amlodipine is the gold standard medication for hypertension in cats. A veterinary formulation (Amodip) is also available

One study assessing amlodipine use in 59 hypertensive cats found cats with a higher SBP at diagnosis required higher doses of amlodipine, but blood pressure control was still achieved.

Clinically significant hypotension following amlodipine administration to truly hypertensive cats is unlikely. Amlodipine can be used together with telmisartan if required.

Theoretically, amlodipine can worsen proteinuria in hypertensive cats due to preferential dilation of the afferent arteriole, which could allow transmission of high systemic BP to the glomerulus. This does not appear to occur however and overall, amlodipine causes a reduction in proteinuria, likely due to the decrease in SBP that occurs with treatment.


Amlodipine has been reported to cause ginigival hyperplasia in cats but remains the gold standard for hypertenstion control

It is important not to introduce CCB/RAAS inhibitor treatment to dehydrated, unstable CKD cats as glomerular filtration rate may drop significantly if these drugs are given prior to hydration.

Adverse effects are rarely seen with amlodipine but may include gingival hyperplasia with prolonged administration.

Amlodipine 0.625-1.25 mg/cat q 12-24 h or 0.125-0.25 mg/kg q 12-24h
In cats with refractory hypertension, dosage can be increased to 0.25-0.5 mg/kg q24h

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Diltiazem reduces BP in cats, however the effect is short lived. As amlodipine is more efficacious with less cardiac effects it is the better choice.

Angiotensin receptor blockers (ARBs)

Angiotensin II receptor blockers (otherwise known as angiotensin II receptor antagonists, AT1 receptor antagonists or sartans) modulate the renin-angiotensin system. The angiotensin receptor blocker (ARBs) **telmisartan** effectively reduces SBP in cats. Angiotensin receptor blockers inhibit angiotensin II action via antagonism of the angiotensin II receptor.

Telmisartan displaces angiotensin II from its binding site at the AT_1 receptor. By preferentially targeting AT_1 receptors, this may help prevent vasoconstriction, aldosterone release, sodium and water retention and glomerular hypertrophy.

Additionally, “ACE-escape”, the phenomenon of gradually increasing levels of angiotensin II in patients chronically treated with ACEi, may be avoided. It appears well accepted by most cats and excretion is independent of kidney function. Treatment results in a dose dependent decrease in mean arterial BP and reduced proteinuria within the first 7 days of treatment.

Mild and transient GI signs (e.g. regurgitation, vomiting, diarrhoea) are reported and rarely, liver enzyme elevation was detected. This normalized when treatment was stopped. Telmisartan may also be used in conjunction with amlodipine. It is available as a once daily oral solution in Europe and Australia. It has recently demonstrated efficacy in reducing systolic arterial blood pressure (SABP) in hypertensive cats with SABP >160mmHg and <200 mmHg.

Telmisartan 2mg/kg q24h

In a study of 285 client owned cats with hypertension receiving either 2 mg/kg telmisartan or placebo once daily, telmisartan resulted in reduction in SABP of 20 mmHg compared to baseline by day 14 and by 25 mmHg by day 28. Approximately 50% of telmisartan treated cats had SABP <150 mmHg by day 28. No clinically relevant changes in blood urea nitrogen, creatinine or potassium were detected.

Another study identified similar SABP changes in 221 hypertensive cats that received either telmisartan or placebo. No clinically relevant changes in biochemical parameters were identified. Vomiting was reported in 50% of the telmisartan treated cats (compared with 40% in the placebo treated group) but was single, transient and resolved without treatment. Hypotension associated with clinical signs occurred in 7 cats throughout the study period.

Losartan appears ineffective at reducing SBP when used in conjunction with enalapril in cats with induced CKD.

Angiotensin-converting enzyme inhibitors (ACEi)

ACEi reduce both systemic and glomerular hypertension, but provide only modest antihypertensive effects (reduces SBP by <15 mmHg), making them unsuitable for monotherapy. ACEi may increase potassium and creatinine concentrations due to GFR reduction following efferent arteriole dilation. Increases 30% above pre-treatment baselines or inappetance associated with ACEi administration warrant treatment cessation. Benazepril (0.25-0.5mg/kg PO sid-bid) may be better tolerated than enalapril (0.2-0.7 mg/kg sid-bid) as biliary excretion compensates for reduced renal clearance. Still, the risk of adverse effects due to reduced GFR exists for both.

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Other potential treatments

Beta-blockers reduce BP by decreasing heart rate, stroke volume and renin inhibition. **Atenolol** is not an effective antihypertensive in cats.
The aldosterone receptor antagonist, **spironolactone**, is typically used with amlodipine in the management of hypertension and hypokalaemia, associated with hyperaldosteronism (Conn's syndrome). Beneficial effects in cats with CKD and hypertension are unknown.

Ongoing management of hypertension

Hypertensive cats will typically need life-long treatment with multiple treatment adjustments. Ongoing monitoring is essential and after stabilisation should be performed at least every 3 months.

A recent large retrospective study of almost 350 000 cats attending primary care practices in the UK were assessed and 282 cats were identified as hypertensive. Cats diagnosed as a result of monitoring of pre-existing disease had improved survival compared to cats diagnosed after clinical signs of hypertension were recognised. Cats that had an amlodipine dose change had improved survival compared to those with no dose change. This information suggests that regular blood pressure monitoring in cats may decrease the morbidity associated with hypertension.
Systolic blood pressure <120 mmHg and clinical signs of weakness or tachycardia may indicate hypotension or disease progression prompting further investigation.
Reducing SBP to below 160 mmHg may prevent cats from developing new ocular lesions and improves hyphaema and retinal oedema. Retinas may reattach, although whether vision will return is unpredictable. Even if vision is restored, subsequent retinal degeneration in response to the previous hypertensive episodes may result in permanent vision loss.

In a retrospective study of 88 client owner cats with hypertensive chorioretinopathy, 57.6% of eyes (note not cats!) that were declared blind at presentation regained some vision following treatment.

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