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ARTICLE TITLE

Hypertension: why it is critical

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KEY WORDS

Hypertension; cat; feline; “target organ”; TOD, “blood pressure”

KEY POINTS

1) Hypertension is common, particularly in older cats and those with co-morbidities such as chronic kidney disease, acute kidney injury and hyperthyroidism
2) Blood pressure measurement should be considered in at risk cats; those with co-morbidities, cats exposed to pharmacological agents or toxins associated with hypertension and those over nine years of age
3) Target organ damage (TOD) affecting the eyes, brain, heart/vasculature and kidneys have all been documented in cats and the rationale for treatment is to prevent TOD occurring
4) Treatment should always be administered even if TOD has already been documented, as there is evidence that treatment can ameliorate TOD, including retinal reattachment and regain of vision.

SYNOPSIS

Hypertension is a common problem, particularly in older cats. Hypertension secondary to a concurrent disease is the most common form of hypertension in this species, particularly in association with chronic kidney disease or hyperthyroidism. However, idiopathic hypertension may account for up to 24% of cases. Any form of persistent hypertension risks target organ damage (TOD) to the eyes, brain, kidney and myocardium/vasculature, therefore measurement of blood pressure is vital in at risk cats to try and identify occult hypertension before TOD occurs. This article addresses when and how to perform blood pressure measurement in cats, TOD that has been documented in this species and our evidence basis for treating hypertension.

Introduction

It is vital to think about the possibility of hypertension in cats that may be at risk of this condition, because patients rarely have overt warning clinical signs. It is devastating for your patient (and their owner) if they lose their sight due to a condition that wasn't checked for, but so easily could have been (see Figure 1). Untreated hypertension also puts the other target organs at risk of damage, resulting in increased morbidity and mortality. This condition is common; a recent epidemiological study of cats in the UK found an incidence risk of 19.5%.[1] This article will discuss how we define hypertension, which cats are at risk, when to monitor blood pressure (BP), and how we can apply evidence-based medicine to treat this condition.

Defining hypertension

Although it is possible to measure systolic arterial blood pressure, diastolic arterial blood pressure and to calculate mean arterial blood pressure, measurements of systolic arterial blood pressure (SBP) are considered to be the most reliable in cats and are therefore used for recommendations of when to treat and how to monitor for treatment response. Studies that have tried to establish what a "normal" SBP is in healthy cats have had varied results, but one study that measured blood pressure in almost 780 healthy cats in a rehoming center found the median SBP was 120mmHg (interquartile range 110-132mmHg).[2] This study also found that median SBP increased with age in healthy cats, with cats $\geq$ 9 years of age having significantly higher SBP than cats aged 3-9 years, although the difference between the median measurements was only approximately 10mmHg. The proportion of cats that developed hypertension also increased with advancing age in a study of healthy cats and cats with CKD.[3] However, not all studies have found consistent results regarding age and increasing blood pressure.[4,5]

The latest ACVIM guidelines[4] on hypertension define the following categories for SBP:

- Normotensive < 140mmHg: risk of target organ damage (TOD) is minimal
- Pre-hypertensive 140-159mmHg: risk of TOD is low
- Hypertensive 160-179mmHg: risk of TOD is moderate
- Severely hypertensive > 180mmHg: risk of TOD is high

These categories can only be guidelines as blood pressure will inevitably vary day-to-day and depending on circumstances. Care must be taken when measuring SBP to try and minimize the effect of situational hypertension (discussed below). However, these categories help provide a framework for the diagnosis and treatment of hypertension.

Types of hypertension

There are generally three categories of hypertension: situational (or white coat) hypertension, idiopathic (or primary) hypertension and secondary hypertension.

Situational hypertension

Cats can be prone to situational hypertension, in which stress increases SBP through autonomic nervous system alterations on higher centers of the central nervous system. It is difficult to quantify exactly how much stress can increase SBP. In the previously mentioned study of 780 healthy cats in a rehoming center, SBP was lowest in cats that appeared calm during the measurement (median 112.8mmHg), increased significantly in cats deemed "cooperative but anxious" (median 123.2mmHg) and was significantly higher again in cats that were "nervous, excited or aggressive" during BP measurement (median 131.6mmHg).[2] The main concern is that situational hypertension could lead to a false diagnosis of true hypertension and unnecessary treatment. If you obtain a high BP reading, this should prompt fundic examination to look for supportive evidence that true hypertension is present (discussed further below). However, a normal fundic exam cannot definitively rule out hypertension

and at present the search for biomarkers that can confirm the presence of hypertension has been unrewarding.[6] Measurement of elevated BP on one occasion, without evidence of hypertensive retinopathy should be confirmed at another consultation within 1-2 weeks. It appears that cats adapt quickly to having BP measurement performed and a repeated measurement on a subsequent visit can often be lower; in three recent randomized, placebo-controlled studies for treatment of hypertension, 18-28% of cats in the placebo arm achieved a reduction in SBP of $\geq$ 15% or to < 150mmHg by 28 days.[7-9] There is no evidence to suggest situational hypertension should be treated in cats. However, the consequences of not treating true hypertension can be severe. Therefore, if a cat demonstrates persistently elevated SBP (> 160mmHg) on repeated measurements on different occasions, anti-hypertensive medication should be initiated.

Another consideration is which cats should have BP measurement performed. It has been suggested that BP measurements should be initiated in cats from 3 years of age every 12 months, to start obtaining baseline readings for the individual animal.[10] However, as with any test, the likelihood of a type 1 error, (i.e. a false positive), is increased with a lower prevalence of disease. Therefore, measurement of BP in young healthy cats in which the prevalence of hypertension is very low will inevitably produce false positive results that provide a clinical conundrum for the clinician: to treat, or not to treat? One study of 137 healthy cats aged 0.7-16.6 years found 21.9% of the cats had an SBP measurement that would assign them to the ACVIM "Hypertensive" category with moderate risk of TOD, and no association was found between SBP and age.[5] However, none of the cats had fundic examination and repeat measurements were not performed to help rule out situational hypertension. Additionally, four cats had an SBP >180mmHg, but three of these were under 3 years of age and were subsequently removed from the analysis, highlighting the difficulty of deciding what to do with young cats that are seemingly hypertensive. As a result, the ACVIM consensus statement argues that screening for hypertension is reasonable on an annual basis from 9 years of age, but should not be

performed in younger animals,[4] although consideration could be given to performing a fundic examination on a regular basis in cats of all ages as part of a complete physical examination.

Steps should be taken to minimize stress and to reduce the type I error rate of diagnosing hypertension by considering the following points:

- Only measure blood pressure in patients considered to have a possibility of having hypertension due to:[4]
    - The presence of clinical abnormalities consistent with hypertensive TOD
    - A diagnosis of a condition known to be associated with hypertension
    - Treatment with a pharmacological agent (e.g. erythropoietin, darbepoetin alfa) or ingestion of a toxin known to be associated with hypertension (e.g. cocaine, methamphetamine, 5-hydroxytryptophan; although hypertension associated ingestion of these toxins has only been reported in dogs to date).
    - An older cat (≥ 9 years of age) with possible occult disease
- Reduce possible stress factors as much as possible (e.g. having a quieter and calmer environment for monitoring blood pressure or allowing more time for acclimatization before measuring).

A summary of which cats should have BP measurement performed is shown in Box 1.

Idiopathic hypertension

Idiopathic hypertension seemingly accounts for approximately 13-24% of feline hypertension,[11-13] however, this is a diagnosis of exclusion and it is possible these percentages are over-estimates. If hypertension is diagnosed in a patient without a known underlying cause, this should prompt diagnostics to ensure there are no concurrent conditions resulting in secondary hypertension.

Secondary hypertension

Secondary hypertension occurs in conjunction with another disease process or due to a medication or toxin that elevates blood pressure. This is the most common type of hypertension in cats.[4,10] The exact etiology of hypertension in association with concurrent disease is incompletely understood. In other species, chronic activation of the renin-angiotensin-aldosterone system (RAAS) is known to play a role, however studies have failed to identify increased plasma renin activity in either hypertensive CKD cats[14] or in hypertensive hyperthyroid cats.[15] A recent study found polymorphisms in the uromodulin gene to be associated with SBP, but not with renal function or CKD; further work is required to explore the impact of these specific polymorphisms, however they may affect water and sodium handling in the thick ascending limb of the loop of Henle.[16]

Diagnosis of any of the following conditions should prompt measurement of SBP and if hypertension is present the cat requires antihypertensive treatment in addition to treatment of the underlying condition. Conditions associated with secondary hypertension include:

- Chronic kidney disease (CKD): this is the most common cause of secondary hypertension in cats[1,12,13,17] and the prevalence of hypertension with CKD has been documented at 19-61%.[18,19] The cause and effect relationship of CKD and hypertension is complex and discussed in further detail below under TOD.
- Acute kidney injury (AKI): hypertension has also been documented in 58.7% cats with community acquired AKI and was not related to the grade of AKI or serum creatinine.[20]
- Hyperthyroidism: prevalence of hypertension varies from approximately a quarter of cases,[1,12] up to 87% of cats having systolic or diastolic hypertension in one study.[19] Other studies have documented increasing prevalence (approximately twofold) within six months of restoration of euthyroidism, although a proportion of these cats also developed azotaemic CKD.[15,21] There is no association between the prevalence of hypertension and the severity of hyperthyroidism.[22] Therefore, documentation and treatment of hypertension in all hyperthyroid cats at diagnosis and at re-examinations once euthyroid is paramount.

- Diabetes mellitus: an association between diabetes mellitus and hypertension has been made in cats, although prevalence appears to be low. One study of 14 diabetic cats found a zero prevalence of hypertension,[23] whilst another study including 66 diabetic cats found 15% to have hypertension, although this was not a significantly higher proportion than in the control cats.[24] A large epidemiological study of cats with hypertension found 2.1% had a concurrent diagnosis of diabetes mellitus,[1] although additional concurrent diseases may not have been thoroughly excluded. Two cats in a study of hypertensive cats with hypertensive retinopathy had diabetes mellitus, although one also had concurrent CKD.[13] However, it would still be prudent to periodically check for hypertension in the diabetic feline patient.
- Hyperaldosteronism: this is not common but should be suspected particularly if hypertension is documented in combination with hypokalaemia or signs of hindlimb weakness and/or cervical ventroflexion.[25]
- Pheochromocytoma[26] and Cushing's syndrome[27] can both cause hypertension, but are uncommon conditions in the cat.

BOX 1

Which cats should undergo blood pressure measurement?

- Cats with sudden onset blindness or central neurological signs
- Cats newly diagnosed with CKD, AKI, hyperthyroidism, diabetes mellitus, hyperaldosteronism, Cushing's or pheochromocytoma
- Cats already diagnosed with CKD: BP should be checked at diagnosis and at regular intervals (e.g. every 3-6 months)
- Cats at diagnosis of hyperthyroidism, at the point they become euthyroid and at subsequent re-examinations
- Cats already receiving medication for hypertension at all re-examinations
- Cats receiving other pharmaceutical agents (e.g. darbepoetin alfa) or that have had toxin ingestion known to affect blood pressure (e.g. cocaine)

The impact of hypertension

Regardless of the underlying cause, sustained increases in BP cause tissue injury and the aim of treatment is to prevent this damage occurring. The so-called "target organs" are at risk due to the presence of a rich arteriolar blood supply, or via sustained increases in systemic vascular resistance. Damage occurs with loss of autoregulatory mechanisms in arterial blood flow in these organs, which include the eyes, brain, kidney and myocardium.

Target organ damage: the eyes

The retinal vessels share similar physiological characteristics to the encephalic and cardiac microcirculations, therefore examination of the retinal vessels is important to detect changes that may compromise vision as early as possible and also to provide an indication of how hypertension may also be affecting other organs. Lesions that may be apparent with hypertensive retinopathy include haemorrhages, bullous detachments, vessel narrowing and/or tortuosity, and retinal oedema. Occasionally, hyphaema and vitreal haemorrhage can occur and hyphaema can lead to secondary glaucoma. For review of feline hypertensive retinopathy lesions, readers are referred elsewhere.[28] Cats may present with blindness and complete mydriasis and historically, restoration of vision has been considered unlikely,[4] with documentation of some vision being regained in only 13% of blind eyes in one feline study.[13] However, a very recent study found that vision, as assessed by menace response, was regained in 76 of 132 blind eyes (57.6%) in cats with hypertensive chorioretinopathy following treatment of their hypertension.[29] Initial treatment was amlodipine monotherapy in 94% of the cats. Complete retinal reattachment took >60 days in some cases and persistence of vision at last re-examination was actually higher in cats where reattachment had taken >60 days, compared to within 3 weeks.

The vulnerability of the eye to TOD appears variable; blood pressure was significantly higher in cats with retinal lesions in one study of 58 cats (SBP 262 +/- 34mmHg) when compared to other hypertensive cats without retinal lesions (SBP 221 +/- 34mmHg),[30] but lesions have been reported in other studies to occur at SBP elevations as low as 168-170mmHg.[13,17] In humans, choroidal vascular changes appear more common with an acute elevation in BP, whereas retinal vascular changes appear more likely with chronic hypertension.[31] Additionally, hypertension due to renal diseases, particularly glomerular pathologies in humans, results in more severe retinopathies than in those with essential (i.e. idiopathic) hypertension.[32] Hypertensive changes in the eye are seen in approximately 40-60% of geriatric cats with hypertension,[11,12] and appear most common with concurrent CKD.[13,33]

The eye is the quickest (and cheapest!) organ to evaluate for TOD, and fundic examination should be performed to help confirm all cases of suspected hypertension (e.g. if SBP is >160mmHg) so that treatment can be initiated as quickly as possible. One large epidemiological study found that ocular examination was not performed in 38.6% of cats diagnosed with hypertension,[1] suggesting there is a barrier to performing this examination in first opinion practice. There are a number of methods available for performing fundic examination, which have been reviewed in detail elsewhere,[28] but indirect ophthalmoscopy is an inexpensive and rapid method of examining a large field of view and should be widely considered prior to use of a direct ophthalmoscope. For a guide to performing this technique, see Box 2 and Figures 2 and 3.

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BOX 2:

How to perform indirect ophthalmoscopy (see also figures 2 and 3):

- Ask an assistant to help hold the patient and to keep the head still and if needed, to gently open the eyelids.
- Hold a light source against the side of your head and look for a tapetal reflection.
- Once the reflection can be seen, place a 20 dioptre or 2.2 Pan Retinal lens in front of the eye.
- Obtaining an image of the fundus in the lens requires your eye and the light source, the lens and the cat's eye to be in line with each other. Tilting the lens slightly and moving it towards and away from the patient can be tried to improve the image obtained.
- Resting your third or fourth finger on the cat's head or on your assistant's hand can be helpful to improve stability.

Tip:

- Pupil dilation allows a more thorough examination of the fundus and is extremely helpful when less experienced with this technique.
- Placing the cat in a dark room can help to achieve mydriasis, but if this is not sufficient then applying one drop of 1% tropicamide to each eye will usually achieve mydriasis within 15minutes.[34]

Retinal imaging software, such as VAMPIRE (Vascular Assay and Measurement Platform for Images of the Retina) is now starting to be used in cats to analyse vessel widths and arteriolar bifurcations.[35] Application of advanced technology such as this may help improve sensitivity of TOD detection in the future.

<u>Target organ damage: the brain</u>

TOD in the brain can result in hypertensive encephalopathy and appears more likely with a sudden increase in BP, an SBP > 180mmHg, or both.[36] Two of four cats that underwent surgical reduction of

renal mass had an abrupt increase (40-50mmHg) in SBP and developed severe neurological signs of ataxia, blindness, stupor and seizures within 12-18 hours.[37] Post mortem, these cats demonstrated diffuse brain oedema with cerebral arteriosclerosis.

In studies of cats with spontaneous hypertension that have all had hypertensive retinopathy, 29-48% have had concurrent neurological signs including disorientation, seizures, depression, ataxia and vestibular signs.[13,38] Treatment of hypertensive encephalopathy can be successful if initiated early.[36,39] Hypertension accounted for 8.1% of reactive seizures in feline patients in another study, with SBP measurements of 170-186mmHg; satisfactory seizure control was achieved with amlodipine in 3/5 cases.[40]

Target organ damage: the kidneys

Hypertension and CKD are very common co-morbidities; azotaemia is seen in approximately 70% of hypertensive cats[11] and conversely, approximately 60% cats with CKD are hypertensive.[3,19] Additionally, cats that are normotensive at diagnosis of CKD are significantly more likely to develop hypertension over time compared to healthy older cats, although the prevalence of hypertension increases over time in this group too (see Figure 3).[3] One study has suggested that cats with later stage CKD may be more likely to have severe hypertension than cats in IRIS stage 2,[41] but other studies have found no relationship between severity of CKD and severity of hypertension.[3,18,19]

Hypertension contributes to kidney damage; increasing SBP is associated with increasing proteinuria[42] and a higher time-averaged blood pressure is associated with glomerulosclerosis and hyperplastic arteiolosclerosis,[43] i.e. renal injury. Progressive CKD, defined by an increase in plasma creatinine >25% over 12 months, was also associated with proteinuria and with a higher prevalence of hypertension (40%) compared to cats with stable CKD over the same timeframe (29%).[44] Severity of proteinuria is highly correlated with survival time,[42] and antihypertensive treatment can reduce proteinuria[11] even

with amlodipine monotherapy, despite the action of amlodipine to dilate the afferent arteriole, which should increase glomerular pressure. The glomerular pressure change is presumably offset by the larger decrease in systemic blood pressure, although at present it is not clear if the subsequent drop in proteinuria represents a reduction in kidney injury or is a surrogate marker for the changes in glomerular filtration rate induced by both the systemic and glomerular pressure changes.[11,45]

Target organ damage: the heart and vasculature

On clinical examination, 42-74% hypertensive cats have a systolic cardiac murmur[30,38,46] and 13-16% of hypertensive cats have a gallop rhythm.[30,38] Left ventricular hypertrophy (LVH) or an abnormal left ventricular geometric pattern is a common finding in hypertensive cats, affecting 74-85% of cases,[30,46] however, the degree of hypertrophy does not correlate with the severity of the hypertension[46] and cause and effect remains uncertain.[47] Treatment with amlodipine reduced the number of cats deemed to have LVH in one study, but no significant difference in any echocardiographic measurements were found before and after treatment.[46] The effect of telmisartan on LVH in hypertensive cats has not yet been evaluated, however, studies in both humans and rodent models have revealed that telmisartan can directly inhibit cardiomyocyte hypertrophy via its actions on the cardiac angiotensin II receptor.[48] It is therefore possible that in addition to reducing SBP and therefore cardiac afterload, treatment of hypertensive cats with telmisartan may have additional impact on the heart.

The great vessels can also be affected by hypertension. Calculating the ratio of the diameters of the proximal ascending aorta relative to the aortic annulus can be helpful for differentiating hypertensive from non-hypertensive cats.[49] Additionally, severe hypertension (SBP 260mmHg) was thought to be the cause of a dissecting aortic aneurysm in a recent case report of a 10 year old DSH, however investigations into possible causes of the hypertension were not performed.[50] Furthermore, a recent study demonstrated the presence of vasa vasorum arteriopathy in cats with hypertension.[51] The vasa vasorum is the delicate network of arterioles that supplies blood to the walls of the great vessels. This

study included 24 cats, with 46% having a diagnosis of hypertension, however, this was largely based on clinical and/or pathological evaluation as only six cats (four hypertensive) had had their BP measured. Nevertheless, vasa vasorum arteriopathy correlated with hypertension status, the presence of renal arteriosclerosis and degenerative lesions within the great vessels.

Effect on survival time

Counterintuitively, numerous studies have failed to find an association between how well controlled hypertension is with treatment and survival time.[11,12,38,42] Additionally there was no significant difference in survival between hypertensive cats with normal and abnormal echocardiographic findings.[30] However, cats that present for monitoring of concurrent disease have better survival rates than cats diagnosed due to the presence of clinical signs, which presumably reflects owner motivation for monitoring and treating their cat.[1] A major confounding factor to studying survival time is that the vast majority of cats in these studies have been treated for their hypertension. The impact of anti-hypertensive therapy may mask the effect of hypertension on morbidity and mortality, however, withholding treatment would not be ethically acceptable.

Survival times vary slightly between populations: cats still alive 7 days after diagnosis of hypertension in first-opinion practice had a median survival time of 400 days[1]; 24 cats with hypertensive retinopathy had a median survival time of 18 months[38]; whilst another study of 141 hypertensive cats had an overall survival time of only 260 days.[11] In that last study, survival was strongly associated with severity of proteinuria at diagnosis of hypertension. Proteinuric cats with urine-protein-to-creatinine ratio (UPC) >0.4 survived a median of only 162 days, whereas survival time for borderline proteinuric cats (UPC 0.2-0.4) was 313 days and for nonproteinuric cats (UPC <0.2) it was 490 days. Importantly, UPC was shown to significantly decrease with amlodipine besylate treatment in this study.

The greatest barrier to diagnosis

The biggest reason that hypertension is not diagnosed is likely due to BP measurement not being performed. Only 4.4% of cats ≥ 9 years, had BP "assessed" during a two-year period (2012-2013) in a recent study of 347,889 cats in first opinion practice in the UK.[1] Additionally, in some cases the assessment was based on ocular changes (70 cats) or clinical signs alone (five cats) and did not include BP measurement. The most common reason for BP assessment was presentation with clinical signs (63.1%), followed by monitoring of concurrent disease (31.2%). Unsurprisingly given that most cats had to present with clinical signs before BP was measured, over 90% of the cats diagnosed with hypertension were in the "severe" category. Owners of 535 cats were offered BP measurement, but declined.

Waiting for owners to report clinical signs of illness in cats is likely to result in under-diagnosis of a number of common conditions including hypertension. A study of 100 apparently healthy cats aged 6 years and over, found 8 cats had SBP >160mmHg, of which four were borderline proteinuric and one had a heart murmur, although no fundic lesions were reported and repeat SBP measurements on a subsequent visit were not performed.[52]

Furthermore, in a recent online survey of owners of 1089 cats with CKD, only 3% were reported to have concurrent hypertension.[53] As this study was an owner survey, the results will have been subject to self-selection bias regarding participation and it is possible some owners did not realize their cats had been tested for and/or diagnosed with hypertension. However, since other studies suggest prevalence rates of hypertension in cats with CKD of more like 20-65%, either these were very unusual CKD cats, or hypertension was being underdiagnosed in this cohort, which included cats in numerous countries. Creatinine concentration is an independent risk factor for becoming hypertensive,[3] and the frequency of severe hypertension increases as International Renal Interest Society (IRIS) stage

increases in cats with CKD.[41] However, 17% of cats that are normotensive at diagnosis of azotemic CKD can still go on to develop hypertension later.[3] It is therefore recommended that SBP should be measured at CKD diagnosis and if normal, every 3-6 months thereafter. Similarly, given the high prevalence of hypertension at diagnosis of hyperthyroidism (25-87%)[1,12,19] and increasing prevalence following treatment[15,21] it is recommended that SBP should be measured at diagnosis of hyperthyroidism, on restoration of euthyroidism and every 3-6 months thereafter.

Diagnosing hypertension in cats

Tips for performing blood pressure measurement:

- Let the cat acclimatize to the environment for 5-10 minutes, this could be during history taking. Ideally let the cat be in or out of the cat carrier as they prefer but take the top of the carrier off if they are to be allowed to stay in there, so that the SBP measurement can be performed with them in the box.
- If the cat is already hospitalized, then blood pressure could be taken in the kennel if the cat seems relaxed with you doing so.
- However, do not specifically hospitalize a cat for SBP measurement, as this may stress them more.
- Use Doppler or high definition oscillometry (HDO),[54] as traditional oscillometry does not perform reliably in cats.[55] If using HDO, the tail may be the easiest place to place the cuff. The HDO needs to be coupled to a computer to confirm that the pulse waves produce an adequate trace. Further information on this is available elsewhere.[10]
- Try not to shave any fur off (if you have to because the pulse is difficult to find, then they need time to relax again afterwards), instead wet the fur and skin with surgical spirit but try not to get it on their pads because it is cold and they don't like it.

- Have the cat held by the owner if possible, or by someone comfortable and familiar with cats. The restraint should be as light as possible. Place a cuff (width should be 30-40% of the diameter of the leg) around one of the limbs or around the tail.
- Use plenty of gel with your probe to find the pulse and keep the volume of the Doppler machine low or use headphones.
- Inflate the sphygmomanometer to 20-40 mmHg above where the sound of the pulse vanishes and then slowly release the pressure. Ignore the first reading.
- Take 5-7 readings and record them all if possible. If the readings are all trending in one direction, then discount them and take another 5 readings. The aim is to have 5 similar readings and then take the mean of those 5 as your overall reading.
- Record what cuff size and which f used. Repeated measurements on other occasions should ideally have the same person performing the measurement and replicate the same cuff and the same leg or tail.
- An average SBP reading >160mmHg should prompt fundic examination to help differentiate true hypertension from situational hypertension.
- Treatment should be initiated immediately in cats with SBP >160mmHg and evidence of TOD.
- If there is no evidence of TOD then BP measurement should be repeated, ideally within two weeks, and treatment recommended if SBP is still >160mmHg.

Treatment of feline hypertension

There are two first line treatment options for feline hypertension: the calcium channel antagonist amlodipine besylate, and the angiotensin II receptor blocker telmisartan. Both have been evaluated in prospective, randomized, placebo-controlled clinical trials of hypertensive cats with SBP 160-200mmHg that did not have evidence of target organ damage.[7-9] Initial reductions of 20-30 mmHg can be expected with both medications.

Traditionally, the recommended starting dose of amlodipine is 0.625mg per cat q24h PO. However, cats that require a dose increase to achieve adequate control of their hypertension have a higher SBP at baseline,[1,56] and recent evidence suggests that if baseline SBP is >200mmHg a starting dose of 1.25mg per cat q24h PO should be considered.[56] If needed, amlodipine can be increased to a maximum of 2.5mg per cat q24h PO, but this is rarely necessary and should prompt a careful discussion with the owner to check compliance.

The recommended starting dose of telmisartan is 2mg/kg q24h PO in Europe[1] and with an initial 14 days of 1.5mg/kg q12h PO in the USA, then subsequent reduction to 2mg/kg q24h.[2] The dose may need to be decreased at a later date depending on response. There are no current studies comparing amlodipine with telmisartan and treatment choice is largely clinician dependent at present. However, data on the use of telmisartan for cats with SBP >200 mmHg or with target organ damage is currently lacking, excepting one case report of its use in a cat with amlodipine-induced gingival hyperplasia.[57] Treatment with amlodipine has been shown to ameliorate numerous types of TOD. Amlodipine treatment reduced the proportion of cats with ventricular hypertrophy from 11/14 to 6/14.[46] In 70% of cats, sole agent amlodipine reduced UPC by a median of 0.12.[11] Amlodipine treatment can result in resolution of reactive seizures[40] and reduction in other signs of hypertensive encephalopathy and retinopathy.[36] Treatment with amlodipine, when used as a sole agent in 94% of 88 cats with hypertensive choriorentinopathy, resulting in 57.6% cats with bilateral blindness regaining some vision as assessed by the menace response.[29]

Because antihypertensive treatment can reduce proteinuria,[11] the priority in cats that are both hypertensive and proteinuric (UPC >0.4) is to adequately control blood pressure first and then to

[1] http://www.noahcompendium.co.uk/?id=-469656
[2] http://www.semintra.com/pdf/MERL18201%20SEMINTRA%20US%201-page%20PI%20v1c.pdf

reassess UPC to see if additional anti-proteinuric therapy is required. As noted in a small number of cats, the combination of amlodipine with telmisartan appears to be well tolerated,[58] therefore if required, a second agent can be added to the treatment regime.

Interestingly, unlike in humans, dietary sodium chloride supplementation has not been found to affect renal function or blood pressure in either healthy older cats[59] or in cats with nephrectomy models of CKD.[60] However, dietary sodium chloride restriction in feline nephrectomy models can activate the RAAS, reduce GFR and result in urinary potassium wasting,[60] therefore it is prudent to avoid dietary salt restriction in hypertensive cats.

Although widely used as antihypertensive therapy in dogs, angiotensin converting enzyme (ACE) inhibitors are not recommended for monotherapy use in cats with hypertension because the reduction in SBP is typically only around 10mmHg and is therefore unlikely to be sufficient for most cats. Additionally, beta blockers (e.g. atenolol) have limited effect on blood pressure and are not therefore recommended for feline hypertension.

Following initiation of treatment, cats should be reassessed every 7-10 days for blood pressure measurement and dosages tailored to achieve an SBP of <160 mmHg at a minimum and preferably <140 mmHg. However, SBP <110 mmHg or <120 mmHg in conjunction with lethargy/weakness should raise concern for hypotension prompt a reduction in antihypertensive medication dose. SBP should be rechecked on all future examinations if a cat is on antihypertensive medication.

Hypertensive crises

Cats presenting with an acute hypertensive crisis, particularly those with SBP $\geq$ 180mmHg with signs of intracranial TOD require emergency treatment and 24-hour care, therefore referral should be sought if 24-hour care cannot otherwise be provided.[4,10] Intravenous medications are likely to be

required and blood pressure needs to be carefully and gradually decreased. Evidence for medication selection is largely lacking, but a discussion of possible medications can be found elsewhere.[4]

Summary

Hypertension is common in cats, particularly older cats and those with certain co-morbidities. It is crucial that small animal clinicians identify at-risk patients and assess for hypertension before being presented with a patient already showing clinical signs. However, any patient already exhibiting TOD should have treatment initiated immediately, then be carefully re-examined to assess response and change treatment doses as needed. Hypertension that is detected and controlled produces excellent outcomes, with no effect on survival time.

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Figure legends

Figure 1: Complete retinal detachment and mydriasis in a cat that had never previously had blood pressure measurement performed.

Figure 2A: To perform indirect ophthalmoscopy, ask an assistant to gently restrain your patient, hold a light source next to your head and stand nearly an arm's length away from your patient.

Figure 2B: Look for a tapetal reflection and then place your lens between you and the cat's eye, moving it slowly until you see the fundus. In the correct position the fundus will fill the lens.

Figure 3: Kaplan–Meier curve of probability to become hypertensive. CKD; chronic kidney disease, time is in days from first visit. Cats with CKD have a greater probability to be hypertensive at each time point than healthy cats (P<.001). Censored cases are represented by ticks. Figure from "Changes in Systolic Blood Pressure over Time in Healthy Cats and Cats with Chronic Kidney Disease." E.S. Bijsmans, R.E.Jepson, Y.M. Chang et al. JVIM 2015: 29(3); 858