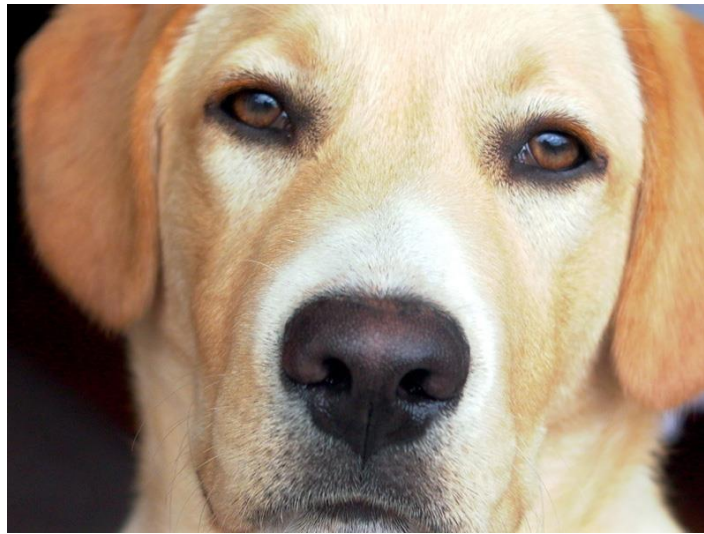


HIGH BLOOD PRESSURE IN DOGS WITH KIDNEY FAILURE



High blood pressure (termed hypertension) is a very common symptom associated with chronic kidney failure (CKF). A veterinary intern study in 2007 by Brown, Atkins and Bagley, *'Guidelines for the Identification and Evaluation and Management of Systemic Hypertension in Dogs and Cats'*, found that up to 93% of dogs with CKF also suffer from high blood pressure.

Hypertension causes further rapid deterioration of renal function and can inflict acute blindness. These facts make it crucial that vets check for high blood pressure when first diagnosing CKF and then begin treatment to lessen symptoms straight away.

When kidney failure is first diagnosed, it's a ticking time-bomb that presents tough challenges for owners as well as the dogs themselves and vets charged with treating them. The problem is the illness has likely been progressing for several months and sometimes years without anyone noticing. Symptoms rarely show until late into the disease. By the time of diagnosis, there may only be days or weeks left to intervene before the kidneys and other organs start to shut down. Intervention can slow progression of the disease if started early enough and, if successful, it can offer greater longevity and an improved quality of life for the dog.

Unfortunately, quite apart from trying to get the primary illness under control through diet and medication, there are often secondary issues to contend with as well. These may include life-threatening complications such as urinary tract infections, kidney and bladder stones, anaemia and hypertension.

When Vets Take a Blood Pressure Check

A dog can become extremely excited and often anxious or afraid by a trip to the vet. The journey to the vets will itself cause their pulse rate to increase, and a throng of dogs, cats and possibly other animals in the waiting room will further stimulate heart rate and blood pressure. By the time they get to see the vet, their blood pressure may have climbed to abnormal levels, which in turn could lead to misdiagnosed hypertension. Dogs need to calm down for a few minutes and an understanding and experienced vet will take their time to get exacting results. It is also advised that vets take at least five blood pressure readings and then average out the multiple for a more reliable test result.

What Causes Hypertension in CKF Dogs?

The problem with any associated and debilitating illness, such as hypertension, is that we may never discover whether it existed before or after the onset of kidney failure. Hypertension is another condition that a dog can suffer from for many years without any necessarily obvious symptoms. However, veterinary science tells us that (unlike humans) dogs very rarely suffer from primary hypertension¹. The condition is almost always secondary and associated with another disease. These include diabetes mellitus, an over-active thyroid, Cushing's disease, tumours of the adrenal glands and renal disease.

Chronic kidney disease has long been recognized as the single most common cause of hypertension in dogs².

Systemic hypertension is a very complex condition with diverse health repercussions. Essentially, blood pressure is detrimentally or beneficially affected by two mechanisms known as systemic vascular resistance (SVR) and/or cardiac output (CO). SVR relates to blood vessels narrowing or expanding, while CO relates to the amount of blood pumping in and out of the heart. Kidney disease alters specific biochemical pathways in the canine body and causes SVR and CO mechanisms to work in an abnormal way. In particular, increased sodium circulating in the blood and abnormal fluid retention will both promote high blood pressure. These would probably be enough on their own to cause a catastrophic effect, but other biochemical pathways are also altered in renal failure that cause blood vessels to constrict, and this further escalates blood pressure.

What Are The Effects Of Hypertension If Left Untreated?

Hypertension creates many problems for blood vessels and other organs, including the kidneys. Haemorrhage of blood vessels causes blood to leak into tissues and this then indirectly causes a loss of circulating oxygen and nutrients, which in turn increases the level of toxins and causes multiple organ damage elsewhere in the

body. The heart is particularly affected because of the added stress. Heart muscles and valves become fatigued and damaged, which means the “pump” no longer pumps as effectively. The heart-rate often increases, causing excessive blood flow. Congestive heart failure is not uncommon. A dog’s brain is also affected by hypertension. In particular, those structures of the brain that deal with vision can haemorrhage and swell, eventually developing into a complete loss of sight or severe ocular damage and disease. Glaucoma and retinal detachment are notable long-term effects.

The kidneys are severely affected. The nephrons that make up the filtering mechanisms either become damaged or are lost completely, which in turn causes an increase in the volume of toxins circulating in the dog’s body. Protein loss is also an effect exacerbated by hypertension and this can lead to further haemorrhage and fluid loss into the lungs and other parts of the body. The pH (acid alkaline) balance is also affected, along with electrolyte conservation and elimination.

Perhaps the greatest problem of leaving hypertension untreated is that it worsens the kidney disease, which in turn worsens hypertension – and this vicious circle of degeneration causes all aspects of general health to decline at an alarming speed.

Identifying hypertension early and then treating it effectively are crucial to prolonging the life of a dog. The first step in this aim is, of course, to insist a vet performs a blood pressure check at the earliest opportunity and then at regular intervals while they manage the kidney disease. Bear in mind that kidney disease can cause hypertension – therefore, just because a dog may not present with it when chronic kidney failure is first diagnosed, it doesn’t mean it won’t develop at a later stage.

The Treatment Debate

One of the big challenges of canine kidney failure is knowing when to treat conservatively with a holistic approach and diet ... and when to treat more aggressively with traditional medicines. The problem with the latter is that most medicines present a Catch-22 dilemma, as they invariably place greater stress on the kidneys due to increased by-product toxins. My opinion is there isn’t a choice in the case of hypertension. Without fast and effective treatment, the kidney disease will affect other organs and systems and a dog’s prognosis and quality of life will rapidly deteriorate. However, it is certainly worth undergoing a period of reducing salt (sodium) intake in the diet, which in turn may control hypertension initially by reducing blood volume and limiting blood flow. Delaying the start of chemical-based drugs might be a worthwhile and workable possibility.

It is also worth mentioning that many studies refer to the sometimes zealous over-expectation of some vets and owners when treating this condition³. Because hypertension involves a dog taking some aggressive medications, many with

adverse side effects, vets and owners should seek to lower blood pressure to acceptable levels but not necessarily to normal levels. The point being, the shortest period a dog is on these drugs the better, as it will help prevent associated complications of long-term use.

When to Start Traditional Treatment

There is a range of different medicines that are able to treat hypertension in dogs. A vet ought to find the most harmful problem (systemic vascular resistance or cardiac output) involved in causing blood pressure to rise, and then prescribe a suitable medication that targets that specific concern. Some thought must also be given to the renal disease itself and how different medications may interact with it, for better or worse. It is noteworthy to mention that corticosteroids, phenylpropanolamine, NSAIDs, and erythropoietin are medications that indirectly raise blood pressure⁴. These treatments are best discontinued or reduced to the smallest doses for a short period to assess whether the hypertension is then relieved and, therefore, more likely associated with the medication and not the kidney failure.

Treatment should begin when systolic blood pressure is greater than 150 mm Hg and/or diastolic pressure is greater than 95 mm Hg. However, note that normal blood pressure is specific to the dog breed. For example, a Labrador will have a blood pressure of around 120/70 while a Chihuahua's normal reading would be around 135/88. It is common for large breeds to have lower than average blood pressure while racing dogs such as greyhounds tend to have higher than average blood pressure. The American and European Societies of Veterinary Nephrology and Urology support what is known as the IRIS staging system for treating hypertension in dogs with chronic kidney failure. This states that anti-hypertension treatment is best started at stage 2 for most dogs, and at stage 3 for all dogs with CKD.

In their 2013 study, *"Treatment of Systemic Hypertension Associated with Kidney Disease"*, Simona Buoncompagni, DVM, MS, DACVIM, and Mary H. Bowles, DVM, DACVIM suggest that evidence of proteinuria (protein in the urine) plays a part in deciding when to start treatment for hypertension. Proteinuria increases the decline of kidney function – and hypertension increases the likelihood of proteinuria – so early treatment of hypertension is generally advocated when both conditions are present. Following IRIS staging system guidance, treatment should begin as early as stage 1 in such cases.

There is a huge array of different medications, all with slightly different routes to controlling high blood pressure. In trying to deal with CKD and hypertension, there are some medications which seem to help both conditions simultaneously - which is certainly an advantage. However, in almost all situations, the use of different drugs in combination proves more successful.

Angiotensin-Converting Enzyme Inhibitors (ACEI)

The mechanics of this group of anti-hypertensive drugs are extremely complex. In essence, they have a profound effect on the neurotransmitters that stimulate the heart and cut cardiac output. In doing so, a reduction in the force of blood pumping through blood vessels occurs, resulting in lower blood pressure. ACEIs are often used because they also have two other functions, one being to control both sodium (salt) and water. This in turn reduces blood volume and again helps lower blood pressure. The second function is to calm muscle-stimulating-neurotransmitter effects, which help relax blood vessels and increase their diameter. The larger the blood vessels become, the lower the pressure of blood flowing through them. ACEIs therefore, benefit the CKF dog by attacking hypertension in three crucial and very effective ways.

Significantly, ACEIs also lower proteinuria, which prevents a consequential decline in kidney failure.

On the down side, ACEIs restrict the successful elimination of BUN (blood urea nitrogen) and creatinine, which means these blood values can rise. Close and regular monitoring is important to prevent acute renal failure occurring. Other adverse reactions common to ACEIs include conversely low blood pressure, abnormally high calcium levels (hypercalcaemia), anorexia and lethargy. These issues make treating hypertension a tricky balancing act for vets, requiring close and careful supervision and a proactive approach to the treatment plan.

The ACEIs of choice for dogs with CKF are Benazepril and Enalapril. Benazepril is probably the better of the two, as there was no evidence of renal toxicity observed in dogs during clinical trials. There is also evidence that Benazepril acts to stimulate the appetite in cats with renal disease⁵ and anecdotal evidence suggests it may offer the same advantage in dogs, where Enalapril tends more often to cause a reduction in appetite.

It is worth noting that my own preference is Benazepril for dogs with renal disease, because in comparison to Enalapril it is cleared 55% by the liver and only 45% by the kidneys. Enalapril is cleared 95% by the kidneys, which puts additional and often unnecessary strain on the organs¹¹.

ACEIs are often used together with calcium-channel blockers (CCBs), partly because the latter can offset the adverse reactions of ACEIs while at the same time enhancing the anti-hypertensive action of such medications.

Calcium-Channel Blockers (CCBs)

CCBs are commonly cited for controlling hypertension in dogs when ACE Inhibitors alone don't produce the desired effect. This group of medicines work by restricting calcium movement into cells that make up the heart and the walls of blood vessels. In effect, they make it easier for the muscles of the heart to pump and they widen the diameter of blood vessels, which in turn helps reduce blood pressure. Amlodipine

besylate (Norvasc) is one of the most commonly prescribed FDA (Food & Drug Administration) approved CCBs in veterinary use at the time of writing this article.

Interestingly, while ACEIs are the recommended first line of treatment for hypertension in dogs⁶, followed by a CCB if the ACEI doesn't fully solve the problem – the complete reverse is true for cats.

Beta Blockers

A dog's pulse rate can have a severe effect on blood pressure if it is faster than a normal dog's pulse rate. The pulse (heartbeat) ordinarily fluctuates according to the type of activity, just the same as a human being. It slows down slightly when a dog is sleeping – and increases when it is playing, walking or becomes excited. However, some dogs have an abnormally fast pulse rate, which persists even during rest. Hypertension occurs because there is more oxygenated blood being pumped through and out of the heart than the body actually needs for routine activities. Beta block medication affects neurotransmitter molecules in the muscles of the heart, preventing them from being triggered too often. This slows the heart beat and helps reduce blood pressure. Obviously, beta blockers should only be considered when a dog's pulse rate is consistently too fast. Propranolol (Inderal) and Atenolol (Tenormin) are two examples of this type of medication commonly prescribed for dogs.

Alpha Blockers

Alpha blockers are the third best line of treatment after ACE Inhibitors and Calcium Blockers. These medications widen the walls of blood vessels (without affecting heart muscle) by reducing the effect of adrenergic receptors. The net result is lower blood pressure. Alpha Blockers such as Prazosin and Phenoxybenzamine are often prescribed in addition to ACE Inhibitors and Calcium Blockers, but they can also be used separately from these alternative treatments. Side effects to look out for include urinary incontinence, vomiting, anorexia, tachycardia (fast pulse rate) and hypotension (abnormally low blood pressure).

Hydralazine

This is a useful vasodilator that is often used in emergency situations because it is fast-acting. It is commonly given following transplant surgery to help lower blood pressure in cats. Dogs are given this medication orally to relax blood vessel walls. A reduction in blood pressure occurs due to the improvement in blood flow. This is a rapid-acting aggressive drug, which means vets looking for the therapeutic level should prescribe it at the lowest possible dose and titrate upwards.

Recently Introduced Drugs Of Some Significance

There are always new drugs entering the market. Many have recently been used to good effect in human kidney failure and consequential hypertension, but their effects on dogs are sometimes untested or lack reliable study data. It takes years for some drugs to become confirmed as safe and effective, which means while the following may seem promising they are not necessarily the safest, best, most readily available or affordable options for consideration at the current time.

Carvedilol

This drug has also been used successfully in humans to treat hypertension and mild to severe congestive heart failure. It has both antioxidant properties and a joint alpha and beta blocking effect, with fewer side effects than the two drugs taken individually. In high doses, it also acts as a calcium blocker.

The FDA has approved the drug for treating human hypertension (since 2006) in a controlled release formulation, although it is only rarely ever prescribed for dogs and is not yet approved for use in dogs (2015). It is available under the names Carvil, Coreg, Dilatrend, Kredex, Eucardic, and Carloc. The potential for toxicity and the uncertainty of therapeutic dosing regimens is a concern, which means it will take more testing and study to assess the value of this drug in canine kidney disease and hypertension.

Some studies conducted on rats⁷ seem to show renal function remains stable during prolonged treatment, although this in itself is insufficient as canine and rat physiology is similar but not the same. A very small study⁸ on dogs conducted in 2002 showed small doses (0.2 mg/kg) didn't have any effect on hypertension or renal function, while both were clearly diminished at higher doses (0.4 mg/kg). Positive effects might be achieved through cautious and small dose increases.

Aldosterone Inhibitors

Aldosterone is a hormone involved in the exchange of sodium and potassium in many areas of the body, including the kidneys. Due to its inflammatory actions, it seems to play an important role in kidney failure and blood vessel constriction (which can lead to hypertension). There have been some minor studies showing how restricting this hormone might help in controlling hypertension in cats⁹, but there have been no comparable studies on dogs. While this is a promising avenue of research, there is a huge amount of further exploration and examination needed before the role of aldosterone and its inhibition is better known and understood.

Spironolactone (Aldactone) is sometimes given to help control salt and fluid build-up and stiffening of the heart muscle. This is a human version of an Aldosterone Inhibitor.

Angiotensin Receptor Blockers (ARBs)

Angiotensin receptor blockers (ARBs) work much like ACEIs, although their use in canine kidney failure and associated hypertension remains unknown and controversial. Studies using the drug Losartan¹⁰ (a popular ARB) show reductions in intraglomerular hydrostatic pressure, systemic blood pressure, and end-organ damage occur in dogs with induced renal disease. There is some evidence that suggests ARBs are helpful in canine CKD and associated hypertension, and may help reduce proteinuria, but the long-term effects are as yet unknown and untested.

In Conclusion

Treating chronic kidney disease and stabilizing significant blood levels will always be the highest priority, even though secondary and associated conditions like hypertension need addressing as soon as they present themselves. The point being that alleviating the symptoms of CKD will often relieve these secondary conditions and create the potential for reducing the need for aggressive and potentially toxic medications.

The first step towards this goal is to get a dog's blood pressure checked – and then confirm a diagnosis of hypertension by re-checking at regular intervals over a short period. The second step is for vets to prescribe the most suitable medication according to the type of hypertension presented, and then assess whether that medication has worked or whether a multi-drug treatment is more likely to get the condition under control. The sooner this can be achieved, the better, because hypertension will not only make the kidney disease deteriorate but also allow further conditions to develop.

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