Hypertension in Small Animal Kidney Disease

Harriet Syme, BVetMed, PhD, FHEA, MRCVS

Key Words
- Sodium retention
- Chronic kidney disease
- Renin-angiotensin-system
- Hypertension

Kidney disease is an important cause of hypertension in many species. It is often considered separately from primary (so-called essential or idiopathic) hypertension. This approach may be flawed; however, because many of the mechanisms that are proposed to cause hypertension in patients with kidney disease may also play a role in the pathogenesis of primary hypertension, and vice versa. It may also result in renal hypertension being considered as a single pathologic entity, with uniform underlying cause, which is unlikely to be the case.

This article reviews the mechanisms that are currently considered to be of greatest importance in the pathogenesis of hypertension and how best to treat the condition. Methods of blood pressure measurement and descriptions of the end-organ damage that occurs in dogs and cats with hypertension (in organs other than the kidney) are not described in this article. These topics have been the subject of numerous reviews, and readers are referred to those for information on these topics.1–4

Control of Blood Pressure

The long-term control of blood pressure is possible by a complex mixture of neural, hormonal, and intrinsic factors involving the brain, heart, vasculature, and especially the kidneys. The rudiments of this control mechanism are summarized in Fig. 1. Extracellular fluid volume varies in line with total body sodium content. A primary function of the kidneys is to regulate sodium and water excretion, and consequently, they play a dominant role in the long-term control of blood pressure. The 2 predominant mechanisms of renal regulation of blood pressure are pressure natriuresis and the renin-angiotensin-aldosterone system (RAAS). These systems are augmented by the sympathetic nervous system and the influence of numerous vasoactive mediators acting at both local and systemic levels.

Pressure Natriuresis

Pressure natriuresis is a system that regulates the amount of extracellular water by coupling the excretion of salt and water in response to changes in blood volume.
and cardiac output, which are detected as alterations in renal perfusion pressure. The kidney acts as a servocontroller with infinite negative feedback gain; essentially, when functioning normally, it is able to adjust blood pressure back to a normal level regardless of the magnitude of the initial deviation. Regulation of sodium excretion is achieved through control of glomerular filtration, tubular reabsorption, and tubular secretion, which are processes that are controlled by biophysical characteristics such as transcapillary pressure gradients as well as a variety of hormones and locally acting vasoactive substances.

Disruption of the pressure natriuresis relationship is a fundamental aspect of hypertension in all experimental models of hypertension and in naturally occurring disease. Guyton and colleagues showed in a series of experiments in the 1980s that if the renal arterial pressure was maintained at a normal level (due to a hydraulic occluder placed around the aorta) infusion of vasoactive hormones such as angiotensin II, aldosterone, or vasopressin caused significant increases in systemic pressure and signs of volume

---

**Fig. 1.** Integrated control mechanisms of arterial blood pressure. Solid arrows indicate positive effects; dashed arrows, negative effects. Ang-II, angiotensin II; ANP, atrial natriuretic peptide; [Ca^{2+}]_{i}, intracellular calcium ion concentration; EDCFs, endothelium-derived constricting factors; EDHF, endothelium-derived hyperpolarizing factor; EDRFs, endothelium-derived relaxing factors; ET-1, endothelin 1; HR, heart rate; NO, nitric oxide; OLF, ouabainlike factor; PGI_{2}, prostacyclin; PKC, protein kinase C; SNS, sympathetic nervous system; TXA_{2}, thromboxane A_{2}. 

---
overload. When the suprarenal aortic constriction was relieved, natriuresis and diuresis occurred, and the hypertension was ameliorated.

In patients with kidney disease, the capacity of the kidney to excrete sodium may decrease, resulting in an increase in salt sensitivity concomitant with an increasing incidence of hypertension. This mechanism for hypertension is particularly important in patients with end-stage renal disease with extreme reduction in glomerular filtration rate (GFR) resulting in a decrease in the amount of sodium that is filtered at the glomerulus. With lesser degrees of kidney dysfunction, any reduction in the filtered sodium load should be offset by a reduction in tubular sodium reabsorption in any remaining functional nephrons. This suggests that the hypertension in patients with milder forms of chronic kidney disease (CKD) is linked to impairment of sodium handling in the collecting duct, whereas alterations in sodium handling in more proximal parts of the nephron allow compensatory mechanisms to maintain sodium balance, dysregulation of sodium transport in the distal nephron may not allow counterregulatory mechanisms to operate.

It has been hypothesized that defective sodium excretion in hypertension could be caused by vasoconstriction of the afferent arteriole. This vasoconstriction could be mediated by mechanisms involving vasoactive substances, that is, either excessive production of vasoconstrictors, such as endothelin, or impaired vasodilation, for example, due to impaired release of nitric oxide (NO). Alternatively, the vasoconstriction could result from increased sympathetic tone or activation of the renin-angiotensin system (RAS). This mechanism is not specific to patients with kidney disease but could also be operative in patients with primary hypertension.

RAAS

The RAAS directly controls peripheral vascular resistance and renal reabsorption of sodium and water. Renin is secreted from juxtaglomerular cells in response to reduction in effective circulating fluid volume. This condition is detected by reduction in arterial pressure, renal perfusion pressure, or chloride delivery to the macula densa. Adenosine, acting via adenosine 1 receptors, mediates the inhibition of renin secretion in response to both increased chloride delivery to the macula densa and increased renal perfusion pressure as detected by baroreceptors in the afferent arterioles. Both cyclooxygenase 2 and neuronal NO synthase mediate increases in renin release in response to low blood pressure. Renin is also released in response to increased sympathetic nerve stimulation via β₁-adrenoceptors. Renin release can be inhibited by the action of angiotensin II on juxtaglomerular cells.

Renin is an aspartyl protease that is synthesized in the juxtaglomerular cell as a proenzyme, prorenin. Prorenin is converted to renin exclusively within the juxtaglomerular cell, so plasma renin activity (PRA) is undetectable following bilateral nephrectomy. Renin cleaves angiotensinogen, produced by the liver, to yield a decapeptide angiotensin I. Then, angiotensin I is converted to the octapeptide angiotensin II by the angiotensin-converting enzyme (ACE), which is located on endothelial surfaces and in the circulation. Other metabolites of angiotensin I and II can be formed by ACE-2, a homolog of ACE. Some of these metabolites have effects that oppose those of angiotensin II, resulting in vasodilation and antiproliferative effects. Inhibition of ACE-2 worsens glomerular injury and promotes proteinuria in mouse models of diabetic nephropathy.

Prorenin is secreted constitutively by juxtaglomerular cells, resulting in plasma levels that are about 10 times higher than those of renin. Although this proenzyme was previously considered to have no physiologic role, a receptor, located on
mesangial and smooth muscle cells, has now been identified that binds both prorenin and renin with equal affinity. Once bound to the receptor, prorenin exhibits catalytic activity, enabling conversion of angiotensinogen to angiotensin I. Receptor binding also activates intracellular signaling pathways (eg, ERK and transforming growth factor β). Prorenin may be of particular importance in the pathogenesis of diabetic nephropathy.

Angiotensin II acts on at least 2 different receptor subtypes: type 1 (AT1) and type 2 (AT2) receptors. The AT1 receptor mediates all the classical physiologic effects of angiotensin II. The functions of the AT2 receptor are less well understood, but in general, AT2 receptors seem to oppose the effects mediated by AT1. Angiotensin II increases blood pressure in several different ways, each of which is mediated by binding to the AT1 receptor. It causes immediate and powerful vasoconstriction, thereby increasing peripheral vascular resistance. It stimulates sodium reabsorption in the proximal tubule (via the sodium hydrogen exchanger isoform 3) and also possibly in other nephron segments. Angiotensin II also stimulates aldosterone synthesis and secretion by the zona glomerulosa of the adrenal gland. Aldosterone in turn stimulates reabsorption of sodium by the principal cells of the collecting duct.

Although the effects of RAAS stimulation in mediating hypertension and kidney injury have been generally ascribed to the actions of angiotensin II, there is increasingly substantial evidence that aldosterone may also play a key role. Many of the pathologic changes in the rodent remnant kidney model (eg, hypertension, glomerulosclerosis, and proteinuria) can be replicated by infusion of aldosterone, even when the actions of angiotensin II are pharmacologically inhibited. Conversely, in partially nephrectomized rodents, concurrent adrenalectomy ameliorates the attendant hypertension.

In addition to the circulating RAS, many tissues, including those of the kidney, can generate angiotensin II (and other components of RAS) locally. This tissue-based system can function independently of the circulating hormones and is thought to act in a paracrine manner. Upregulation of the intrarenal RAS may play a pathologic role in progression of some forms of kidney disease. This system may explain the apparent paradox that in some disease states, notably, diabetic nephropathy, there can be an exaggerated hemodynamic response to treatment with ACE inhibitors in spite of low PRA.

**Sympathetic Nervous System**

Inappropriate sympathetic drive may contribute to the development of hypertension. Excessive sympathetic drive results in sodium retention, renin stimulation, and diminished kidney function. The kidney itself plays a role in the generation of increased sympathetic activity by way of renal somatic afferent nerves directly linked to neural cardiovascular control centers in the midbrain. The kidney is therefore both a target and a contributor to increased sympathetic nerve activity.

Increased sympathetic nerve activity is evident even in mild compensated CKD. It is present in models of mild acute kidney damage and in individuals with polycystic kidney disease (PKD) with normal GFR. These observations suggest that sympathetic activation rather than being a consequence of uremia is an early event in the pathophysiology of CKD and that various forms of kidney damage activate the sympathetic nervous system via the afferents of renal sensory nerves.

Kidney transplant recipients with excellent graft function display increased sympathetic nerve activity similar to that of patients undergoing hemodialysis, whereas transplant recipients who undergo bilateral nephrectomy have normalized sympathetic
nerve activity not different from healthy control subjects.\textsuperscript{25} Sympathetic hyperactivity in human patients with CKD has been associated with an increased risk of adverse cardiovascular events.\textsuperscript{26} In the 1950s (before the advent of effective pharmaceutics), it was shown that lumbar sympathectomy could be an effective treatment for malignant hypertension.\textsuperscript{27} Because of the recent development of less-invasive techniques for sympathectomy, there is now a recrudescence in interest in this treatment for human patients with resistant hypertension.\textsuperscript{28,29}

Renalase is a soluble monoamine oxidase that may be relatively deficient in patients with CKD, resulting in increased norepinephrine levels and consequently hypertension.\textsuperscript{30} Renalase is predominantly expressed in glomeruli and proximal tubules, although it is also expressed in cardiac and skeletal muscles. Under basal conditions, it lacks enzymatic activity; however, physiologic stimuli, such as increases in blood pressure, increase its amine oxidase activity. Renalase is readily detectable in the plasma of normal humans but not in patients with uremia. Single nucleotide polymorphisms in the renalase gene have recently been associated with essential hypertension in man.\textsuperscript{31}

Other Mechanisms

Concentrations of parathyroid hormone correlate with blood pressure in human patients with kidney disease.\textsuperscript{32} Chronic hyperparathyroidism may lead to accumulation of calcium inside vascular smooth muscle cells, enhancing their sensitivity to norepinephrine.\textsuperscript{33} This effect can be blocked by treatment with calcium-channel blockers.\textsuperscript{32} However, in one study, parathyroidectomy did not alter blood pressure in patients who underwent kidney dialysis, thus arguing against an important role for this mechanism in the pathogenesis of hypertension in patients with kidney disease.\textsuperscript{34}

Administration of erythropoietin may increase blood pressure.\textsuperscript{35} This finding may be the reason why the use of this drug to achieve a relatively high packed-cell volume target in human patients with kidney disease was associated with an increased risk of adverse cardiovascular events in recent clinical trials.\textsuperscript{36} These effects may occur independent of any viscosity changes that result from increasing hematocrit; it has been suggested that a direct effect on arteriolar constriction may be responsible,\textsuperscript{37} although increased sensitivity to norepinephrine has also been demonstrated.\textsuperscript{38}

PATHOGENESIS OF HYPERTENSION IN RENAL DISEASE

In humans, hypertension is considered to be both a cause and a consequence of CKD. The prevalence of hypertension is reciprocally related to GFR; the worse the kidney disease, the more likely that hypertension will be present.\textsuperscript{39} It is important to recognize that no single mechanism is preeminent in the pathogenesis of hypertension in human patients with CKD but that the relative importance of the myriad mechanisms described earlier varies according to the particular form of kidney disease that is present. A few of the diseases that are of comparative interest in companion animals are discussed in more detail.

Patients who Undergo Dialysis

More than 90\% of human patients with end-stage renal disease are hypertensive before the initiation of dialysis. In most human patients receiving maintenance hemodialysis, hypertension is caused by extracellular fluid expansion. Blood pressure can be controlled by adjusting the rates of ultrafiltration during dialysis and by restriction of dietary sodium intake. The importance of volume homeostasis in these patients is illustrated by results from the Tassin hemodialysis unit where long slow dialysis
treatments are performed, and within a few months of starting dialysis, fewer than 5% of patients require antihypertensive medications for control of blood pressure. Dry weight (in which blood pressure remains normal both before and after dialysis sessions) is more often achieved in this system because the ultrafiltration rate is relatively low, blood-volume changes are relatively small, and intradialysis symptoms are in frequent. This contrasts with results from most dialysis centers, where the prevalence of hypertension remains high in spite of treatment.

In a minority of patients who undergo hemodialysis, blood pressure is refractory to maneuvers directed at volume homeostasis. In these patients, excessive stimulation of RAAS seems to be the mechanism underlying the persistent hypertension. In a seminal study performed in the 1960s, Vertes and colleagues found that maintaining dry weight helped control hypertension without medication in 35 of 40 (87.5%) hypertensive patients who underwent dialysis. In the remaining 5 patients (12.5%) in whom blood pressure remained elevated, PRA was significantly increased and they were designated as having renin-dependent hypertension. These patients were successfully treated (without antihypertensive medication) by bilateral nephrectomy that reduced PRA to undetectable levels.

Hypertension is common in dogs with severe acute kidney failure requiring dialysis. In a study of 153 dogs receiving dialysis treatment at the University of California, Davis, California, 78% had systolic hypertension (>150 mm Hg), 84% had diastolic hypertension (>95 mm Hg), and 87% had either systolic or diastolic hypertension. In that study, hypertension was not significantly related to the cause of kidney failure or to urine output and did not alter survival. Another study also found that the blood pressure before initiating treatment was not related to survival in dogs receiving dialysis.

In a study of 119 cats receiving hemodialysis at the same center, 40% were hypertensive (systolic blood pressure [SBP] >150 mm Hg) before the initiation of dialysis. Blood pressure was not related to the cause of the kidney failure.

**Renal Transplant Recipients**

Several factors are known to contribute to the development of hypertension in human kidney transplant recipients; among the most important factors are immunosuppressive therapy, renin secretion from the native kidneys, transplant renal artery stenosis, allograft dysfunction, and hypertension in the donor. Cyclosporine is commonly incriminated in the pathogenesis of posttransplant hypertension. Cyclosporine (and other calcineurin inhibitors) causes constriction of the preglomerular afferent arterioles, resulting in a decrease in renal blood flow and GFR. Several mediators have been implicated in this process, including endothelin, prostaglandins, inhibition of NO synthase, and activation of RAS. Chronic cyclosporine nephrotoxicity is characterized by the presence of structural lesions in the kidney, predominantly interstitial fibrosis and tubular atrophy. This condition is accompanied by reduction in GFR and systemic hypertension. Development of structural lesions may be prevented by treatment with calcium channel blockers, suggesting that vasodilation of the afferent arterioles may ameliorate the chronic nephrotoxicity of cyclosporine. Glucocorticoids may also contribute to the development of hypertension in transplant recipients.

Renal artery stenosis is a relatively frequent cause of hypertension and allograft dysfunction in humans, occurring in 5% to 10% of kidney transplant recipients. It may present at any time but is most common between 3 months and 2 years following transplant. It may develop due to trauma to the donor or recipient vessels during the transplant, immune-mediated endothelial injury of the donor renal artery, or extension of atherosclerosis from the recipient’s iliac artery. Renovascular hypertension in renal
transplant recipients is the clinical correlate of the Goldblatt one-kidney one-clip model of hypertension that was first described in experimental dogs; hypoperfusion of the single functioning kidney causes stimulation of RAS that in turn causes sodium retention and extracellular volume expansion. These changes improve renal perfusion and reduces RAS activation to levels that are normal or low but inappropriate in relation to the degree of plasma volume expansion. Postglomerular arteriolar constriction maintains GFR at near-normal levels in spite of reduced renal blood flow caused by an increase in filtration fraction.50

In humans, transplanting a kidney from a donor with a familial history of hypertension results in a greater increase in blood pressure in the recipient than when the donor’s family is normotensive.51 The importance of the donor kidney has long been studied in experimental models. Kidney transplant from genetically hypertensive rats causes hypertension in the recipients, whereas renal grafts from genetically normotensive donors lower blood pressure in genetically hypertensive recipients.52 Results of these studies reinforce the primacy of the kidney in the pathogenesis of hypertension.

Severe acute hypertension is common in the immediate perioperative period following a kidney transplant in cats.53 Before the advent of perioperative blood pressure monitoring, many cats that underwent kidney transplant developed postoperative neurologic complications, most often seizures, and these cats often died as a result.54,55 Stupor, ataxia, and blindness have also been reported. Treatment of hypertensive cats with hydralazine reduces the incidence of postoperative neurologic complications.53 In 2 case series, severe hypertension reportedly developed in 21 of 34 (64%) and 9 of 30 (30%) cats that underwent kidney transplant, with blood pressure cutoffs of more than 170 and 160 mm Hg, respectively, to signify severe hypertension in each of the studies.53,56 The reason for the apparent difference in the incidence of postoperative hypertension in the 2 case series is not clear. Schmiedt and colleagues56 postulated that this difference may be related to the cold-organ storage techniques for preservation of the grafts before being transplanted because stimulation of the intra-renal RAS has been documented in rat kidneys subjected to ischemia-reperfusion57 and production of such vasoactive mediators might be reduced at lower temperatures. However, in an experimental study, 10 cats were subjected to kidney autotransplant and contralateral nephrectomy, and none of the cats developed significant postoperative hypertension.58 Renin activity was not increased in these cats following ischemia-reperfusion.59 It therefore seems unlikely that ischemia and reperfusion injury is responsible for the development of hypertension following kidney transplant in cats.

The long-term prevalence of hypertension in cats that have received renal allografts and survived the perioperative period has not been reported. Histopathologic evaluations of donor kidneys from cats dying following kidney transplant have shown minimal arteriolar changes suggesting that hypertension may not be a frequent problem.60 However, in the same study, changes consistent with cyclosporine nephropathy were documented. Cyclosporine concentration has been positively associated with resistive index in cats following kidney transplant, although this change was not associated with an increase in systemic blood pressure.56

Kidney transplant is infrequently performed in dogs, except as an experimental model for transplantation in humans. In one report of 15 clinical cases that underwent a kidney transplant, it was reported that the majority had intraoperative hypertension that was managed with opioids, although one dog also required treatment with nitroprusside.61 One dog developed hypertension following surgery and was treated by removing the remaining native kidney 2 months after it was transplanted; however, whether or not there was resolution of the hypertension was not reported. It is not stated explicitly but seems that the remaining dogs were normotensive.
**Diabetic Nephropathy**

Diabetes is the most common cause of CKD in humans, accounting for approximately one-third of all cases. Hypertension often develops before any detectable reduction in GFR. Once diabetic nephropathy is established, there is a reduced ability of the kidney to excrete sodium and the systemic RAS is suppressed, although the intrarenal RAS may be simultaneously activated. Many humans with type 2 diabetes are characterized as having the metabolic syndrome comprising insulin resistance, hypertension, hyperlipidemia, and obesity. Development of this syndrome is multifactorial, with both genetic and environmental influences playing a role. Hypertension may be caused or exacerbated by the accumulation of glycosylated end products within the endothelium, altered vasomotor activity, increased oxidative stress, and sympathetic overactivity.

Hypertension (SBP>160 mm Hg, mean BP>120 mm Hg or diastolic blood pressure >100 mm Hg) was reported in 23 of 50 (46%) dogs with diabetes mellitus in one study. Several of these dogs were also proteinuric. In another report blood pressure of 31 dogs with diabetes mellitus was reportedly greater than that of healthy dogs, although the difference was small. Mean (SE) SBP of the diabetic dogs was 142.6 (3.89) mm Hg, so it seems unlikely that many of the dogs were overtly hypertensive, although those data were not reported directly. The kidney function of the dogs was not assessed. There are isolated case reports in the veterinary literature of diabetic cats presenting with signs of hypertensive retinopathy. However, there is currently no convincing evidence that diabetic cats are at increased risk for developing systemic hypertension. Blood pressure measurements have been reported in 2 small case series including, in total, 24 cats. None of the cats had an SBP more than 180 mm Hg or were reported to have kidney dysfunction.

**Hypertensive Nephrosclerosis**

Hypertensive nephrosclerosis is reported to be the second most common cause of CKD in humans, accounting for 21% of adult CKD cases. The diagnosis of hypertensive nephrosclerosis implies that hypertension is the cause of the kidney disease, although this remains controversial. One problem is that hypertensive nephrosclerosis refers to a histologic diagnosis (with features including glomerulosclerosis, medial thickening of the arteriolar wall, and intimal fibrosis), but, in fact, biopsy specimens are rarely obtained in this patient subgroup and the pathologic features are, anyway, not specific to hypertensive injury. In addition, although the fact that malignant hypertension causes kidney failure in humans has been accepted for decades, the importance of mild-to-moderate or benign hypertension as a cause of kidney failure is still debated. Although some epidemiologic studies have indicated that hypertension is associated with subsequent development of kidney failure, these studies have been criticized for the fact that preexisting renal disease was not tested for at study entry. This fact essentially means that the hypertension could accelerate the progression of undetected kidney disease in the study participants rather than actually initiating a disease process in otherwise healthy kidneys.

Two seemingly contradictory pathophysiologic mechanisms have been proposed for the development of hypertensive nephrosclerosis. The first putative mechanism is glomerular ischemia. This mechanism occurs as a consequence of chronic hypertension, causing narrowing of preglomerular arteries and arterioles, with a consequent reduction in glomerular blood flow. The second mechanism is glomerular hypertension and glomerular hyperfiltration. It is proposed that hypertension causes some glomeruli to become sclerotic. As an attempt to compensate for the resultant loss of renal function, the remaining nephrons undergo vasodilation of the preglomerular arterioles and
experience an increase in renal blood flow and glomerular filtration. The result is glomerular hypertension, glomerular hyperfiltration, and progressive glomerulosclerosis. These mechanisms are not mutually exclusive and may operate simultaneously in the kidney.

There have been infrequent reports in which histologic features of hypertensive arteriosclerosis have been described in cats with antemortem clinical signs relating to hypertension. However, because kidney disease and hypertension are usually discovered simultaneously in feline patients, it is impossible to determine whether the hypertension could, in some cases, be the cause of the kidney disease rather than vice versa. Although kidney failure is common in cats, there are very few systematic histopathologic descriptions of this condition. Lucke examined 93 cats with gross kidney morphometric changes, only some of which had evidence of functional kidney impairment, and found fibrous arteriosclerotic plaques of the intima and media of interlobar and arcuate arteries. A comparative study of species differences in the development of arteriosclerosis with age also demonstrated a small, but measurable, degree of intimal hyperplasia in older cats. In another small study of cats with kidney failure, medial hypertrophy of the renal arteries was present in 9 of 10 cats examined. These results conflict with those of a study by DiBartola and colleagues on 74 cats with an antemortem diagnosis of chronic kidney failure. No vascular lesions were described in the study, even though 3 cats had retinal detachment, and the investigators concluded that systemic hypertension was the likely cause. The most common histopathologic diagnosis in that study was chronic tubulointerstitial nephritis; the investigators did not comment on whether vascular lesions were not found or simply not considered significant. Blood pressure measurements were not reported in any of these studies. Further advancement of the understanding of the role that systemic hypertension plays in the development or progression of kidney failure in cats requires systematic histopathologic studies. In a preliminary study of kidney specimens obtained at post mortem examination from cats with naturally occurring systemic hypertension histopathologic changes, including glomerulosclerosis, were more marked than in the control group of normotensive cats with CKD. This was in spite of the fact that the hypertensive cats had been treated with amlodipine for months or even years before death. However, whether these changes are the cause or the result of the hypertension (or its treatment) is impossible to determine.

**PKD**

Hypertension in humans with PKD, often developing before any detectable decline in kidney function. Blood pressure is related to renal volume in children and adults. Hypertension may actually accelerate growth of the cysts because effective control of blood pressure with ACE inhibitors seems to retard cyst enlargement. Hypertension is thought to occur in PKD because the enlarging cysts attenuate flow in the renal blood vessels, resulting in areas of local hypoxia. Accordingly, erythropoietin concentrations are relatively increased in hypertensive patients. Although initial studies failed to demonstrate an absolute increase in PRA or angiotensin II levels in patients with PKD, it has subsequently been demonstrated that activation of RAS is increased relative to patients with essential hypertension. It is proposed that because the disease is bilateral, initial activation of RAS is accompanied by sodium retention, which in turn reduces RAS to normal levels, although inappropriate, relative to the degree of extracellular volume expansion. Intrarenal RAS activation has been demonstrated by immunohistochemistry in kidneys that were surgically removed from kidney transplant recipients. Activation of the sympathetic nervous system and increased production of endothelin have also been implicated in the pathogenesis of hypertension in patients with PKD.
Autosomal dominant PKD in cats is the direct clinical correlate of the disease in humans. The underlying mutation in cats is located in the feline PKD1 gene, the homolog of the gene that is affected in 85% of humans with the disease. PKD is not common amongst cats presenting with ocular lesions caused by severe hypertension, although isolated cases may occur. In one small study of 6 cats with PKD and 6 control cats monitored with a directly implanted arterial catheter and a radiotelemetric recording system, no difference in blood pressure was identified. Enalapril was administered to both groups of cats, and an equivalent decrease in blood pressure and increase in PRA was observed in both groups. However, a second study demonstrated that cats with PKD (n = 14) had higher mean blood pressure than gender- and age-matched Persian cats (n = 7), although the SBP and diastolic blood pressure did not differ significantly between the groups and none of the cats were overtly hypertensive. There was a tendency for PRA to be lower in the cats with PKD, and this tendency was reflected by a decrease in the aldosterone to renin ratio compared with the control cats. By analogy with what is found in humans (as described earlier), reduction in PRA does not necessarily indicate that RAS is not implicated in the pathogenesis of any observed increase in blood pressure because RAS should be considered in conjunction with extracellular volume status and PRA should be suppressed if blood pressure is elevated and renal perfusion pressures are increased. It has therefore yet to be conclusively established whether cats with PKD develop hypertension in the same manner as humans.

PKD is infrequently described in dogs but does occur in a population of bull terriers in Australia. Hypertension has not been reported in these dogs, although interpretation of their blood pressure measurements is complicated because many of them have concurrent valvular heart disease.

Glomerular Diseases and the Nephrotic Syndrome

In humans, hypertension is reported to be more common in patients with glomerular than tubulointerstitial diseases and this association is independent of GFR. In patients with nephrotic syndrome, hypertension is common but is usually relatively mild because much of the retained fluid is distributed to the interstitial rather than the vascular space. Historically, it was considered that reduced plasma oncotic pressure caused hypovolemia and sodium retention in the nephrotic syndrome. However, blood volume measurements are generally normal or mildly increased in patients with nephrotic syndrome, and at present it is thought that sodium retention is a primary feature of glomerular disease. Micropuncture studies using experimental models of nephrotic syndrome have localized defective sodium excretion to the connecting tubule and collecting duct. This finding has in turn been linked to aldosterone-independent activation of the epithelial sodium channel and concomitant upregulation of Na+, K+ -ATPase in the basolateral cell membrane. Renal resistance to the actions of atrial natriuretic peptide has also been proposed as an underlying mechanism for the sodium retention that occurs in proteinuric kidney diseases.

Substantial differences have been reported in the prevalence of hypertension in dogs with naturally occurring kidney disease. This disparity is probably in the main because of methodological differences in blood pressure measurement between the studies; however, it has been suggested that, in general, the prevalence of hypertension is higher in the studies in which glomerular diseases predominate. In some cross-sectional studies of dogs with CKD (in which in general, nonproteinuric kidney diseases predominate), correlation between blood pressure and urine protein/creatinine (UPC) ratio has been observed, although in other studies a relationship was not evident. A recent study found that blood pressure in dogs with nephrotic
syndrome was slightly, but significantly, higher than that in the control group with protein-losing nephropathy but without edema or ascites.99

Leishmaniasis is a common cause of glomerular disease in dogs living in endemic areas, notably the Mediterranean basin. In a prospective study of 105 dogs with leishmaniasis, almost half (49.5%) were found to have kidney disease as evidenced by azotemia (creatinine>1.4 mg/dL) and/or proteinuria (UPC ratio >0.5). Of the dogs with kidney disease, 61.5% (n = 32) were reported to be hypertensive with an SBP more than 180 mm Hg (n = 25) or more than 150 mm Hg in conjunction with left ventricular hypertrophy (n = 7).95 Interestingly, the prevalence of hypertension in the dogs that were proteinuric but not azotemic was 70.6% (12 of 17 dogs). Leishmaniasis may serve as a useful naturally occurring model for the further study of systemic hypertension in dogs with glomerular disease.

There are only limited reports of blood pressure measurements from other spontaneously occurring glomerular diseases in dogs. Hypertension (SBP>180 mm Hg) was present in 22 of 69 (31.9%) dogs in which blood pressure was measured before obtaining a kidney biopsy sample; many but not all of these dogs were suspected to have glomerular disease.100 A juvenile glomerulopathy has recently been described in French mastiffs; blood pressure was only measured in 4 dogs, and none were reported to be hypertensive.101 One study reported that only 12 of 146 (8.2%) soft-coated wheaten terriers with protein-losing nephropathy were hypertensive, with 5 of the dogs having retinal lesions; however, it is not clear in how many dogs blood pressure measurements were actually obtained, so the true prevalence of hypertension in this disease remains uncertain.102 Hypertension has been reported in dogs with Lyme nephropathy but again its frequency is uncertain.103

Hypertension has not been reported in association with the membranous glomerulonephritis that is sometimes seen in young, predominantly male, cats.104

CKD of Undetermined Cause

In many veterinary patients in whom CKD is diagnosed, proteinuria is mild and no specific underlying cause for the kidney disease is identified. In many of these patients, the kidneys are small and it is presumed that were a biopsy to be performed (although this is rarely clinically indicated), tubulointerstitial nephritis and fibrosis would be identified. It is in this group of relatively poorly characterized patients, in particular elderly cats, that hypertension is most frequently recognized. In most studies, about two-thirds of cats presenting with signs of hypertension-induced ocular damage are azotemic.65,66,70 However, estimates of the proportion of azotemic cats that are hypertensive are much less consistent, ranging from 19% to 65%.105–107 These widely differing estimates of the proportion of azotemic cats that are hypertensive are probably in large part because of differences in the populations studied and differences in the cutoff points used to define hypertension. An interesting observation is that cats presenting with signs of hypertensive end-organ damage tend to be mildly azotemic.105,106 Similarly, it is relatively uncommon for normotensive cats diagnosed with CKD to subsequently develop hypertension, even if their kidney disease is progressive. This finding is in contrast to the observation in humans that blood pressure is inversely related to GFR.

Ocular lesions caused by systemic hypertension are less frequently encountered in dogs than in cats. Nonetheless, a small number of case reports exist.108 Dogs may be relatively resistant to the development of ocular lesions, even when relatively severe increases in blood pressure occur, so substantiating a diagnosis of hypertension is more difficult in dogs than in cats.95 In studies in which blood pressure measurement has been performed systematically in dogs with azotemic CKD, the prevalence of
hypertension has been reported as 31% and 54% using blood pressure cutoffs of 160 and 140 mm Hg, respectively.96,97 In another study, although blood pressure was higher in dogs with kidney disease than clinically healthy dogs, the difference was small64 and hypertension was reported to be uncommon109; however, estimates of prevalence were not reported.

Hypertensive cats tend to have slightly lower serum or plasma potassium concentrations than normotensive cats, although in the majority the potassium concentration remains within, or only just less than, the laboratory reference range.70,106 A potential explanation for this difference is relative or absolute hyperaldosteronism in the hypertensive cats—a hypothesis that has been tested in several different studies. Jensen and colleagues110 showed that aldosterone concentration was significantly higher in hypertensive cats with kidney disease than in a control population of young normal cats. A limitation of the study is that it is not possible to tell whether the differences observed were because of the study group being hypertensive or other differences between the groups (eg, in kidney function, diet, or age). However, a subsequent study comparing hypertensive and normotensive cats with CKD also indicated that aldosterone concentrations were slightly higher in cats with hypertension, although there was considerable overlap between groups, and in most instances, aldosterone concentration remained within the laboratory reference range.111 Taken together, these observations seem to support a role for hyperaldosteronism in the pathogenesis of hypertension in cats with CKD, although the relative importance of this mechanism, given the very small observed differences, is unknown.

The cause of hyperaldosteronism in patients with CKD is presumed to be increased renin production caused by a subpopulation of underperfused nephrons. However, in the small number of cats with CKD and hypertension in which PRA has been measured, it has been normal or low.110,111 This result suggests that the relative hyperaldosteronism observed in cats with CKD is independent of RAS stimulation. This suggestion is supported by the clinical observation that there is minimal change in blood pressure when hypertensive cats are treated with ACE inhibitors.110 Accordingly, in a study that measured PRA and aldosterone in hypertensive cats before and after treatment with ACE inhibitors, concentrations of these hormones did not change with treatment.112

The idea that hyperaldosteronism plays a role in the development of hypertension in cats with CKD is also supported by the observation that in a small group of cats presented with signs of hypertension, histologic examination of their adrenal glands revealed extensive micronodular hyperplasia of the zona glomerulosa.113 However, a study that compared adrenocortical histopathologic findings in hypertensive (n = 37) and normotensive cats (n = 30) found no difference between the 2 groups, although adrenocortical hyperplasia was common (present in 65 of 67 cats). In addition, 2 cats, both in the hypertensive group, had adrenocortical adenomas.114 Thus, although adrenocortical pathology is common in old cats, it does not, in isolation, explain the development of hypertension; although relative nonsuppressible hyperaldosteronism could be one contribution to a multifactorial cause.

Several other potential mechanisms for the development of hypertension in cats with CKD have been investigated. The syndrome of apparent mineralocorticoid excess occurs when there is decreased conversion of hormonally active cortisol to inactive cortisone within mineralocorticoid-target tissues, such as those of the kidney. This conversion is catalyzed by the enzyme 11β-hydroxysteroid dehydrogenase type 2, and activity of this enzyme is impaired in human patients with CKD.115 Cortisol has great affinity for mineralocorticoid receptors and its concentration is much higher than that of aldosterone; therefore, if conversion of cortisol to cortisone is reduced,
signs of mineralocorticoid excess (hypokalemia and hypertension) develop. To determine whether reduced conversion of cortisol to cortisone could play a role in development of hypertension in cats with CKD, cortisol/cortisone ratios were compared in hypertensive and normotensive cats, but no difference was found. In fact, the cortisol to cortisone shuttle seems to be more effective in cats with CKD than in clinically normal cats. The reason for this potentially adaptive response to kidney disease is unclear.

NO is a vasodilator with an important physiologic role in the regulation of renal blood flow and control of vascular tone. As might be expected, chronic administration of L-NAME (Nω-nitro-L-arginine methyl ester), an inhibitor of NO production, to clinically normal cats causes a significant increase in blood pressure. Reduced availability of NO resulting in endothelial dysfunction has been implicated in the pathogenesis of hypertension and progression of kidney disease. Two proposed causes of NO deficiency in human patients with CKD are L-arginine deficiency (because the kidney is a primary site for its synthesis) and accumulation of endogenous inhibitors of NO synthase, most notably asymmetric dimethylarginine (ADMA). Studies in cats with CKD did not find any evidence for L-arginine deficiency in this species, but ADMA and creatinine concentrations were positively correlated. However, ADMA concentrations did not differ between hypertensive and normotensive cats and there was no correlation between ADMA measurements and SBP. Therefore, although the possibility exists that the accumulation of ADMA in cats with CKD results in endothelial dysfunction, this does not seem to be associated with the development of systemic hypertension.

The observation that PRA tends to be normal or low in cats with hypertension (see earlier discussion) points to a role for sodium retention and plasma volume expansion in the pathogenesis of renal hypertension in this species. The volume status of cats with CKD has not been systematically studied. In one very small study, plasma volume in 4 hypertensive cats with CKD (33.1 mL/kg) was not significantly different from that of the young normal controls (29.3 mL/kg). No normotensive cats with CKD were included for comparison in the study. Further characterization of plasma volume in larger numbers of cats with CKD is required before conclusions can be drawn. However, consideration of volume in isolation is inherently flawed because blood pressure is essentially a function of the degree of vasoconstriction of the vascular bed relative to its degree of filling (the so-called vasoconstriction-volume hypothesis); simultaneous measurement of both volume and vascular tone is required, although difficult in practice. Increased vascular tone may be particularly important in the pathogenesis of hypertension in cats because they show a profound response to treatment with calcium-channel blockers and other arteriolar dilators. This response is much more dramatic than the typical responses observed in dogs or humans.

Changes in sodium intake have a direct influence on blood pressure in human patients with CKD, and this relationship seems to be stronger at low levels of kidney function. The limited studies performed to date in cats do not indicate that blood pressure in this species is generally salt sensitive. However, only small numbers of cats with either naturally occurring or induced renal dysfunction have been included. The salt sensitivity of blood pressure in hypertensive cats with naturally occurring CKD has not been reported and would be an interesting area for study in the future. In clinically normal dogs, increasing salt intake increases total body water with no change in blood pressure. Varying dietary salt intake also does not alter blood pressure in dogs with experimentally reduced renal mass. No studies have been performed in dogs with naturally occurring CKD.
Nonazotemic CKD

As discussed earlier, contrary to expectation, cats are usually only mildly azotemic when hypertension is diagnosed. In all the larger series of hypertensive cats published to date, about 20% of the cats have been nonazotemic and nonhyperthyroid.65,129 Although some of these cats may have had less common causes of hypertension, such as primary hyperaldosteronism or pheochromocytoma, it seems unlikely that this would account for all of these patients. These cats have been described as having idiopathic hypertension. In these cats, the hypertension may be actually primary, unassociated with any underlying disease process, or may be related to underlying CKD that is not severe enough to result in azotemia. It is well documented in human medicine that the prevalence of hypertension increases in patients with kidney disease, even when GFR is normal.39

TREATMENT

Although a reduction in dietary sodium intake is often recommended as an initial step in the management of systemic hypertension in humans, there is no evidence that this intervention is of any benefit in the management of hypertension in cats or dogs because blood pressure does not seem to change in response to sodium restriction/loading. Reduction in sodium intake does, however, result in potentially deleterious effects including activation of RAS and kaliuresis.125 At present, the recommendation for cats and dogs with spontaneous hypertension is to avoid unusually high salt intake without making a specific effort to restrict it.3 It is currently unknown whether administering subcutaneous fluids to patients with CKD will alter blood pressure in hypertension-susceptible individuals. Until more information is available, it seems prudent to reserve this treatment for specific patients with a tendency to become dehydrated without fluid therapy.

Pharmacologic management is the mainstay of treatment of hypertension in both dogs and cats. In human medicine, it has been proposed that the relative activation of RAS should be an important consideration in the selection of initial treatment.130 Drugs that interrupt RAS are likely to be most effective in the treatment of the high-renin forms of hypertension (Box 1). In low-renin forms of hypertension, treatment with drugs that target the sodium volume-mediated mechanisms of hypertension is

Box 1
Classification of antihypertensive agents based on whether their predominant effect is through renin- or volume-dependent mechanisms

- Renin-dependent hypertension
  - ACE inhibitors
  - Angiotensin receptor blockers
  - Renin inhibitors
  - Centrally acting α2-receptor agonists
  - β-Blockers
- Volume-dependent hypertension
  - Diuretics
  - Calcium-channel blockers
  - α1-Receptor blockers
most logical. Moreover, when combining multiple agents to increase efficacy, selecting the combination of a drug that interrupts RAS and a drug with a predominant effect on sodium volume may be more effective than selecting 2 drugs from the same group. For example, treatment of hypertensive humans with thiazide diuretics is commonplace, but this drug results in stimulation of RAS, which blunts the drugs’ efficacy. Combined therapy with an ACE inhibitor improves blood pressure control.

_Treatment of Hypertension in Cats_

The choice of an antihypertensive agent for cats with systemic hypertension is largely governed by the requirement for a dramatic sustained reduction in blood pressure without the development of unwanted side effects and, in general, without the necessity to administer multiple medications. This situation is in contrast to human medicine in which administration of 2 or more drugs is generally accepted, particularly in patients with kidney disease.123

A marked decrease in blood pressure, typically of the order of 30 to 60 mm Hg, can be achieved by treating hypertensive cats with the second-generation dihydropyridine calcium-channel blocker amlodipine.65,131–134 This drug is well tolerated. Although the half-life of the drug in cats has not been measured, its duration of effect seems to be maintained for more than 24 hours, making it suitable for once-daily dosing and meaning that the lack of precision in daily dosing (due to administering fractions of tablets) is not an issue.133,135 The use of a transdermal formulation of amlodipine in hypertensive cats has been reported.136 Bioavailability of the transdermal formulation was only reported to be about 30% of the oral formulation, and it is possible that even this availability was because of the cats’ grooming and ingesting the product from the pinnae. Given the ease with which amlodipine can be administered orally, the requirement for a transdermal formulation seems debatable.

In an experimental model of induced kidney insufficiency and hypertension in cats, diltiazem was shown to decrease blood pressure but the effect was not maintained for 24 hours, indicating that the drug would need to be given at least twice daily for effective blood pressure control.135 Diltiazem is a member of the benzothiazepine class of calcium-channel blockers and would be anticipated to have more cardiac effects than the drugs of the dihydropyridine class, such as amlodipine. Use of diltiazem has been reported in a small number of cats with spontaneous disease, and although some improvement in blood pressure was noted, amlodipine was found to be more efficacious.65

Another vasodilator drug, hydralazine, has also shown efficacy in the treatment of renal hypertension in cats. Use of this drug may be considered in the emergency setting because with parenteral administration, a response may be demonstrated within 15 minutes of administration.53 It has been used to treat hypertension when it develops acutely following kidney transplant. However, in most clinical situations, the time taken to respond to orally administered amlodipine is perfectly adequate, so in view of the increased potential for side effects when treating with hydralazine (most notably, symptomatic hypotension and tachycardia), treatment with amlodipine is generally preferred.

A potential disadvantage of treating cats with kidney disease with amlodipine is that it causes dilation of the afferent renal arteriole. If sufficient reduction in systemic blood pressure is not achieved, intraglomerular pressure could increase. This disadvantage has led to suggestion that drugs with preferential effect on the efferent arteriole be used instead. In this regard, ACE inhibitors and/or angiotensin receptor blockers (ARBs) are considered to be the first line agents of antihypertensive therapy in humans with CKD,137 although evidence exists that the benefit of specific types of drug is not
as important as the magnitude of their antihypertensive effect.\textsuperscript{138} ACE inhibitors have not been demonstrated to be sufficiently effective antihypertensive agents in cats with naturally occurring systemic hypertension to recommend their use, at least as sole therapy.\textsuperscript{56,110,131} Studies of cats with induced kidney insufficiency have demonstrated that ACE inhibitors decrease systemic blood pressure, but the magnitude of the measured effect is very small.\textsuperscript{85,117,139} It is notable, however, that in these experimental settings, hypertension was either absent or mild, and there was no evidence that RAAS was stimulated, which may explain the apparent lack of efficacy of the ACE inhibitor. An alternative explanation is suggested by the observation that a conventional dose of enalapril (0.5 mg/kg every 24 hours) was insufficient to completely block the pressor effect of angiotensin I infusion in experimental cats, indicating that additional pathways for conversion of angiotensin I to angiotensin II may exist in this species.\textsuperscript{140} ARBs have not been used to any great extent in feline medicine. Losartan was ineffective as an antihypertensive agent in cats with experimentally induced renal hypertension.\textsuperscript{135,140}

A variety of drugs were used to treat systemic hypertension in cats before the effectiveness of amlodipine was established. Thus, some limited clinical experience of treating cats with β-blockers, diuretics, and spironolactone exists, but none is currently recommended as first line therapy. β-Blockers have the potential to reduce blood pressure in renal hypertension not only by decreasing heart rate and stroke volume but also by inhibiting the release of renin. However, β-blockers are not very effective in the treatment of hypertension in cats.\textsuperscript{110,141} Although diuretics are frequently administered to hypertensive people, even those with kidney disease, these agents are not recommended in cats with CKD due to the risk of volume depletion and hypokalemia. Given that mild relative hyperaldosteronism has been demonstrated in cats with hypertensive renal disease, treatment with spironolactone is an attractive option. However, the effectiveness of this therapy has been marginal when used as a sole therapy for the management of hypertension, even in cats with aldosterone-secreting tumors.\textsuperscript{142} When spironolactone was used for treatment of heart disease, 4 of 13 cats developed a cutaneous drug reaction; this reaction may also limit its use in patients with hypertension.\textsuperscript{143} In addition to their effects on vascular smooth muscle, it has been proposed that calcium-channel blockers could act directly to reduce secretion of aldosterone by the adrenal gland, so this may be an additional reason to favor this class of drugs.\textsuperscript{144}

The desired end point of antihypertensive therapy in cats with CKD is to minimize the risk of end-organ damage and to maximize the quantity and the quality of life after implementing therapy. Treatment with amlodipine in cats is sufficient to prevent the development of hypertensive encephalopathy and ongoing ocular damage and to stabilize, or reverse, cardiac hypertrophy.\textsuperscript{53,65,134} However, although kidney disease is reportedly the most common cause of death in cats with hypertension,\textsuperscript{131,145} whether treatment of cats with a particular class of drug has additional benefits in terms of slowing the progression of CKD remains to be determined.

In one study of 136 cats with naturally occurring CKD, blood pressure was not independently related to survival, although all the hypertensive cats were treated, which may have affected patient outcome.\textsuperscript{146} However, in an earlier case series in which blood pressure was not controlled (the report predated the discovery that amlodipine was effective), it is notable that many of the cats lived for long periods in spite of the evidence of ongoing ocular injury.\textsuperscript{66} In a further study, 141 hypertensive cats (most of them azotemic) were treated with amlodipine. A composite measure of the cats’ blood pressure while on treatment was calculated over the entire period of follow-up and used to evaluate for an association between the degree of blood pressure control
and survival. No independent association of blood pressure with survival was found. However, the cats with the highest blood pressure (both before and during treatment) tended to be the most proteinuric, and proteinuria was associated with survival. It remains to be determined whether this association between proteinuria and survival is causative. It remains possible that proteinuria is merely a marker for a more rapidly progressive form of kidney disease.

Treatment with amlodipine in hypertensive cats could in theory cause or exacerbate proteinuria because this drug causes greater dilation of the afferent than the efferent renal arterioles, potentially allowing the transmission of high systemic pressures to the glomerular capillaries. However, treatment of hypertensive cats with amlodipine causes a reduction in proteinuria. This change is presumably because of the profound decrease in blood pressure that occurs.

Treatment with ACE inhibitors has been demonstrated to reduce proteinuria in cats with normotensive CKD. As might be expected, reduction in proteinuria is greatest in those cats that are the most proteinuric before treatment. Unfortunately, despite reducing proteinuria, ACE inhibitors have not shown demonstrable benefit in terms of increased survival times or retarded disease progression in normotensive cats with CKD. It is, however, possible that a similar study of hypertensive cats with CKD would yield more favorable results, particularly because hypertensive cats tend to be more proteinuric than their normotensive counterparts. A small pilot study has demonstrated that combination therapy with benazepril and amlodipine is well tolerated by cats but the UPC ratios were not significantly different from those of cats receiving sole therapy with amlodipine.

**Treatment of Hypertension in Dogs**

In dogs the optimal treatment of hypertension has yet to be established. Although there are published studies of the use of antihypertensive agents in normal dogs and in dogs with experimentally induced kidney disease, there are few systematic studies of dogs with naturally occurring renal hypertension. Anecdotally, it is reported that hypertension is difficult to control in dogs. In one study in which 14 dogs with renal hypertension were treated with a variety of antihypertensive agents, blood pressure was controlled (<160 mm Hg) in only 1 dog.

Use of ACE inhibitors is generally considered to be the first line treatment of hypertension in dogs. This is not because these drugs have been found to be particularly effective in reducing blood pressure, but because they are indicated in the management of proteinuric kidney disease. Treatment with ACE inhibitors has been shown to reduce proteinuria and improve patient outcome in dogs with glomerulonephritis, hereditary nephropathy, and CKD. ACE inhibitors slightly reduced blood pressure in a study of dogs with experimentally induced kidney disease. In the same study, glomerular capillary pressure and histologic scores for glomerular and tubular injury were reduced in dogs treated with enalapril.

In general, except in the emergency setting, treatment of hypertension in dogs is staged: an ACE inhibitor is introduced first, and if the response is inadequate, a second agent, usually amlodipine, is added. Amlodipine is generally preferred to other arteriolar dilators because its use is associated with minimal reflex tachycardia. Combination therapy with an ACE inhibitor and amlodipine may be rational because the former blunts the stimulation of RAS caused by amlodipine. However, even when used in combination, the change in blood pressure (at least in normal dogs) is small. The dose of amlodipine is typically sequentially increased to the maximum recommended dose (Table 1), with adjustments made on a weekly to fortnightly basis. The half-life of amlodipine in dogs is reported to be 30 hours, so it is advisable to make more rapid
adjustments to the administered dose\textsuperscript{156} and also unnecessary to administer it more than once daily. Gingival hyperplasia has been reported in a small percentage of dogs treated chronically with amlodipine.\textsuperscript{157} Otherwise, the drug is generally well tolerated.

A significant proportion of hypertensive dogs seem to be relatively refractory to treatment. In these cases, it is difficult to know what therapeutic regimen should be followed; certainly there is no evidence base to guide therapy. If the patient is tachycardic, then administration of a low dose of atenolol may be logical. Otherwise, a different vasodilator (hydralazine or phenoxybenzamine) can be substituted for the amlodipine to see if it is more effective. The impetus to reduce blood pressure in these refractory cases tends to be the evidence of nonrenal end-organ damage, such as ventricular hypertrophy, or retinal changes. In some cases without end-organ damage, at least in the author’s opinion, the risks of further therapy are difficult to justify. However, there is a risk that uncontrolled hypertension will accelerate progression of the patient’s kidney disease.

In a remnant kidney model of kidney failure in dogs, blood pressure was related to both proteinuria and severity of renal morphologic lesions (mesangial matrix accumulation, tubular lesions, and fibrosis) at the termination of the study.\textsuperscript{158} GFR tended to increase over time following the kidney insult; however, this increase was less evident in the dogs that had the highest blood pressure.\textsuperscript{158} In dogs with naturally occurring CKD, hypertension has also been related to progression of kidney disease. In one study of 45 dogs, the median survival times of dogs in the high–blood-pressure (>161 mm Hg), medium–blood-pressure (144–160 mm Hg), and low–blood-pressure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Dose in Cats</th>
<th>Dose in Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>Calcium-channel blocker</td>
<td>0.625–1.25 mg/cat q 24 h</td>
<td>0.1–0.4 mg/kg q 24 h</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Calcium-channel blocker</td>
<td>10 mg/cat q 8 h (regular formulation)</td>
<td>0.5–2.0 mg/kg q 8 h (regular formulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg/kg q 12 h (sustained release)</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>ACE inhibitor</td>
<td>0.25–0.5 mg/kg q 12–24 h</td>
<td>0.5–1.0 mg/kg q 12–24 h</td>
</tr>
<tr>
<td>Benazepril</td>
<td>ACE inhibitor</td>
<td>0.5–1.0 mg/kg q 12–24 h</td>
<td>0.25–0.5 mg/kg q 12–24 h</td>
</tr>
<tr>
<td>Ramipril</td>
<td>ACE inhibitor</td>
<td>0.125 mg/kg q 24 h</td>
<td>0.125 mg/kg q 24 h</td>
</tr>
<tr>
<td>Atenolol</td>
<td>$\beta_1$-Adrenergic blocker</td>
<td>6.25–12.5 mg/cat q 12–24 h</td>
<td>0.25–1.0 mg/kg q 12–24 h</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Direct arteriolar dilator</td>
<td>1.0–2.5 mg/cat q 12–24 h</td>
<td>0.5–3.0 mg/kg q 8–12 h</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>$\alpha$-Adrenergic blocker</td>
<td>Not recommended q 12 h</td>
<td>0.25–2.5 mg/kg q 12 h</td>
</tr>
<tr>
<td>Prazosin</td>
<td>$\alpha$-Adrenergic blocker</td>
<td>Not recommended q 12 h</td>
<td>0.5–2.0 mg/dog q 12 h</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Aldosterone antagonist</td>
<td>1–2 mg/kg q 12 h</td>
<td>1–2 mg/kg q 12 h</td>
</tr>
</tbody>
</table>

With the exception of the dose for hydralazine in the cat, all other drugs are administered orally. If a dose range is given, treatment is usually initiated at the low end of the range and titrated upward to effect. Once the maximum dose is reached, an additional agent may be added in some instances (see text for details).
(<144 mm Hg) groups were 425, 348, and 154 days, respectively. There was a statistically significant difference in survival between the high- and low-blood-pressure groups. Differences in survival were mainly attributable to progression of kidney disease in the dogs with the highest blood pressure. It is notable, however, that the dogs with the highest blood pressure also tended to be those that were the most proteinuric. Another study has also reported an association between hypertension and/or proteinuria and shortened survival times. Thus, in dogs, as with cats, it is difficult to differentiate the effect of blood pressure and proteinuria on survival; it is possible that the dogs that are the most hypertensive (and proteinuric) have a type of kidney disease that is inherently more rapidly progressive. In humans with kidney disease, the importance of blood pressure control depends on the severity of proteinuria.

**SUMMARY**

> The pathogenesis of hypertension is multifactorial. Uncontrolled hypertension leads to end-organ damage in both dogs and cats. Early recognition and treatment are the keys to preventing end-organ damage.

**REFERENCES**


