

# Blood Pressure in Small Animals - Part 2\*: Hypertension - Target organ damage, Heart and Kidney

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## \*INTRODUCTION

In the last issue of EJCAP [18 (2)] we published the first paper of the series on Blood Pressure in Small Animals. This first paper largely dealt with the assessment of Blood Pressure. Part 2 deals with Target organ damage (TOD). Heart and Kidneys. Part 3 will be featured in the October 2009 issue of EJCAP and will deal with Target organ damage Eyes and CNS

## What is hypertension?

Hypertension is a sustained elevation of blood pressure that is higher than "normal" for that patient. As routine measurements are not done in all clinics, we cannot always refer to the individual's normal blood pressure but have to compare it to either breed specific values or according to normal ranges established by the Veterinary Blood Pressure Society and ACVIM Hypertension Consensus Group.[1] Rather than speak of mild, moderate or severe hypertension it is better to refer to the risk of endorgan/target organ damage (TOD). Hypertension is not only a symptom of a disease but also a disease in itself as it causes damage, mainly to the eyes, the heart, the kidney and the brain.

Risk categories	Systolic Pressure	Diastolic Pressure	Risk for target organ damage
I	<150	<95	minimal
II	150-159	95-99	mild
III	160-179	100-119	moderate
IV	≥180	≥120	severe

It is important to judge systolic and diastolic pressure individually as we can differentiate between

- isolated systolic hypertension: only systolic blood pressure is high, diastolic is normal

- isolated diastolic hypertension: only diastolic blood pressure is high, systolic is normal
- mixed hypertension: both, systolic and diastolic blood pressure are elevated

Each type of hypertension occurs in dogs and cats and each type can cause TOD.

## What type of hypertension can be found in dogs and cats?

Dogs and cats, unlike human beings, suffer predominantly from secondary hypertension. That means that there is an underlying disease causing blood pressure to rise. In some individuals it is not possible to diagnose an underlying problem; these cases are best referred to as "Idiopathic Hypertension". [1]

### **The Kidney and Hypertension**

Chronic renal disease (CRD) is a relatively common problem in small animal patients, especially older cats. Renal disease is also the most common cause of hypertension in small animals. The prevalence of hypertension with renal disease is difficult to establish, some studies have suggested prevalences as high as 60%. [2] A recent study in a first opinion practice determined that approximately 18% of cats were hypertensive when initially diagnosed with chronic renal disease. [3] This study only looked

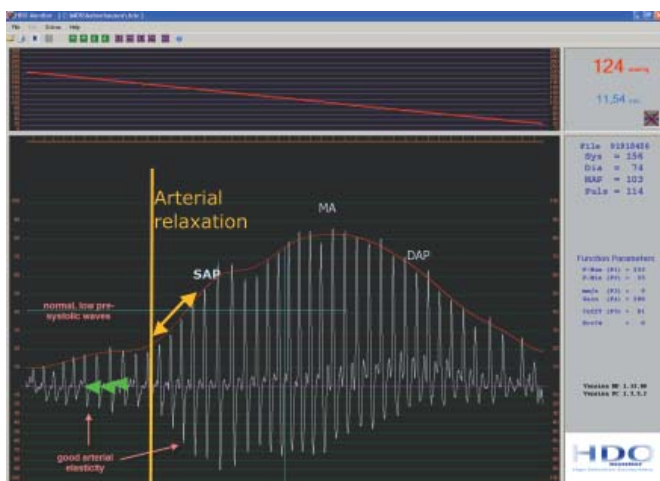
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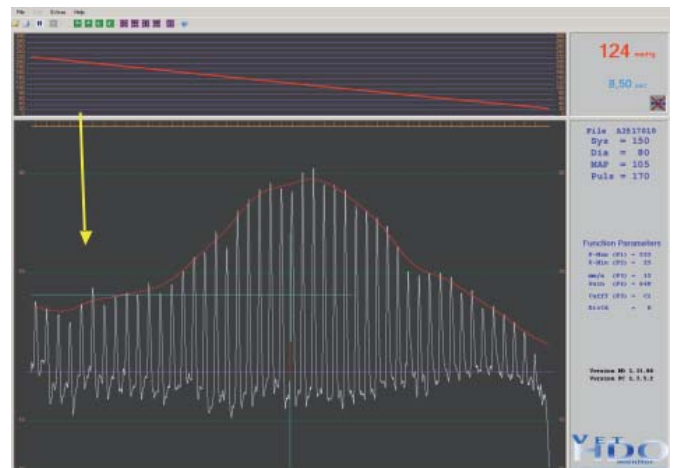
at systolic pressures however so that any diastolic hypertensives would have been missed. How many animals with renal disease go on to develop hypertension is unknown. Data in dogs with spontaneous CRD is conflicting with some studies finding few hypertensives whereas others suggest it is common. [4,5] In dogs it has been shown that the presence of hypertension with CRD is associated with a more rapid decline in renal function and shorter lifespan than dogs with normal blood pressure.[5] In experimental renal injury in dogs relatively minor differences in blood pressure between groups (approximately 20 mmHg systolic, 15 mmHg diastolic) were associated with significantly worse outcomes.[6] In cats the effect of hypertension on outcome is less clear with research suggesting that initial systolic blood pressure and response to antihypertensive therapy are not indicative of survival.[7,8] These studies in cats have however a major limitation in that only systolic blood pressures were measured. By having only systolic values a significant amount of blood pressure information is not available. Not only can diastolic blood pressure be an important factor affecting outcomes, but pulse pressures at presentation have been associated with renal function decline in humans with essential hypertension.[9] Before the degree of hypertension, renal function, and control of hypertension can be definitively related to outcome it is important to gather data on systolic as well as diastolic blood pressure to get a more complete picture of blood pressure status.

The genesis of hypertension in CRD is most likely multifactorial. Most of the data regarding the pathophysiology of hypertension is gleaned from studies on lab animals or humans. In humans both chronic renal failure and glomerulonephritis is associated with hypertension. Possible mechanisms for hypertension include volume overload, renin-angiotensin-aldosterone system (RAAS) activation (systemically as well as locally in the kidney), sympathetic overactivity, increased intracellular calcium, elevated parathyroid hormone levels, and endothelial dysfunction.[10] Angiotensin II and aldosterone contribute to impaired arterial elasticity, as shown in Fig. 1.

*Fig 1 Angiotensin II and aldosterone contribute to impaired arterial elasticity*



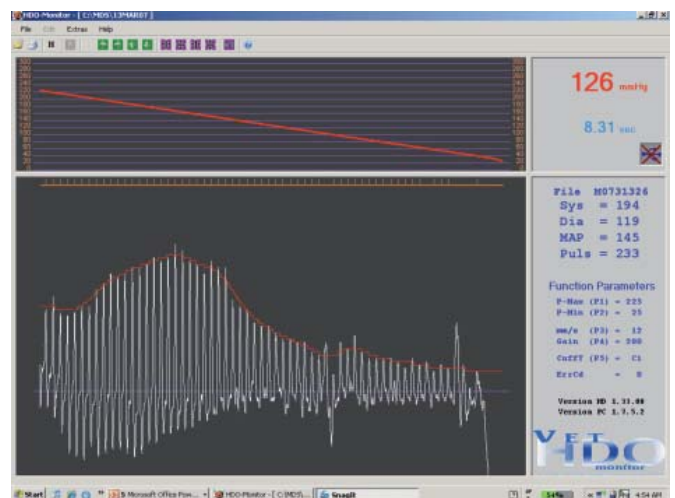
*Fig. 1a: An HDO graph showing the oscillometric pattern in a normotensive patient.*



*Fig. 1b Increased amplitude of presystolic waves indicates of impaired arterial elasticity*

Potential reasons:

Angiotensin II mediated vasoconstriction (will disappear with ACEi treatment) or arterial remodelling (Angiotensin II and/or aldosterone related)



*Figure 1c. HDO trace of a dog with severe hypertension secondary to chronic renal disease. Note the markedly increased amplitude of the presystolic waves indicative of decreased arterial elasticity.*

Chronic renal disease has been associated with a loss of renal autoregulation. Renal autoregulation refers to the ability of the kidney to maintain relatively constant intraglomerular pressures over a wide range of systemic blood pressures. This allows glomerular filtration rate and renal blood flow to remain relatively constant. Loss of autoregulation in renal disease has two major clinically important effects. First it means that remaining glomeruli are subjected to higher pressures when the patient is hypertensive (hyperfiltration) leading to more rapid deterioration of renal function. Secondly it means that the kidney is less able to deal with lower blood pressures resulting in loss of GFR and RBF at pressures that would not cause such an effect in animals with normal kidney function. Loss of autoregulation has been documented in dogs undergoing  $\frac{3}{4}$  or  $\frac{7}{8}$  nephrectomy.[11] Loss of autoregulation has been found in humans and various

lab animal models of hypertension, however autoregulation can be restored through the use of angiotensin converting enzyme inhibitors (ACEi).[12] Alternatively, aggressive lowering of systemic blood pressure will also minimize glomerular hyperfiltration.

### The Heart and Hypertension

Hypertension affects the heart in a variety of ways; however cardiac changes in hypertensives can at times be caused by the diseases that are the underlying etiology of the hypertension. As an example hyperthyroidism can cause hypertension, however the metabolic changes that occur with this disease also have a direct effect on the heart.

In hypertension, the most common cardiac change is the development of left ventricular hypertrophy (LVH) and abnormal valvular motion and loading sequences.

This is an adaptive response to the increased pressure load on the heart. This increased pressure load leads to increased left ventricular wall stress. The Law of LaPlace can be used to understand wall stress(Fig 2);

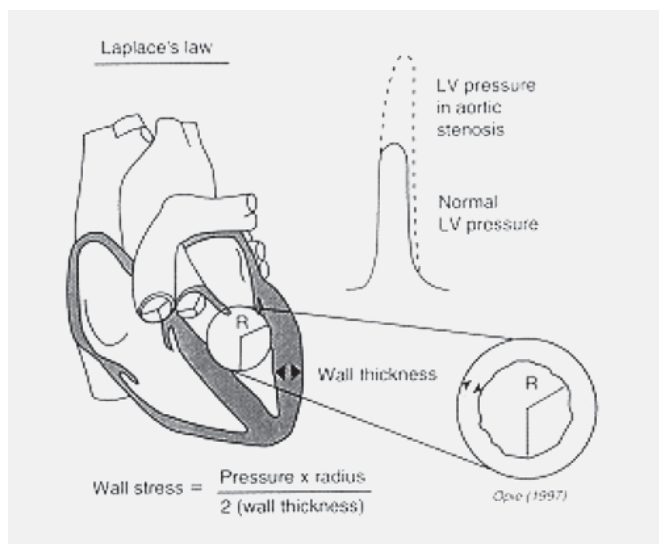


Fig 2

$$\text{Wall stress} = \frac{\text{end diastolic pressure} \times \text{radius}}{\text{Wall thickness}}$$

Wall stress can be increased by increased intracavitary pressures (more severe hypertension) and by increases in the radius of the internal diameter of the left ventricle (for example with dilated cardiomyopathy). If wall stress is increased, an increase in wall thickness (compensatory hypertrophy) will minimize this. The increased wall stress with hypertension is sensed by cardiomyocytes and nonmyocytes which then initiate the processes by which a variety of signals such as growth factors, intermediate peptides (e.g. endothelin and angiotensin II), interleukin 6 related cytokines (cardiotrophin I), and insulin like growth factor I are generated that lead to changes in the myocardium.[13] Both myocardial hypertrophy and myocardial hyperplasia occurs. The result of both is more or less marked wall thickening (concentric left ventricular hypertrophy) and

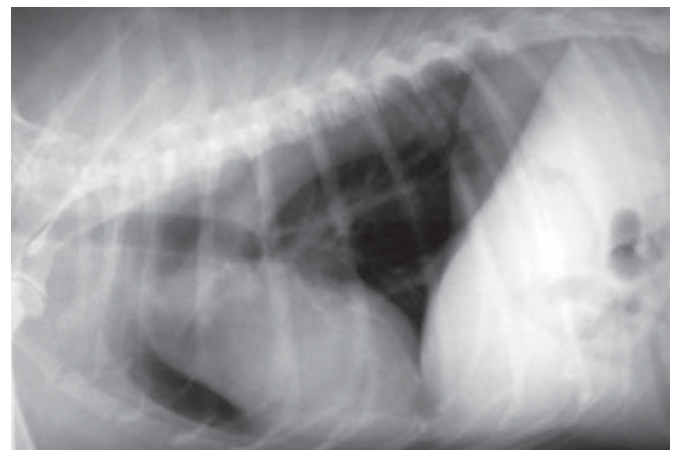
increase in heart muscle mass and abnormal diastolic function. In the patient with hypertension, LVH can have significant negative effects. One such negative effect is the tendency toward a variety of arrhythmias that has been documented in humans.[14] With LVH there is often a mismatch between myocardial oxygen demand and supply, potentially resulting in ischemia. Collagen synthesis leading to fibrosis is commonly seen resulting from growth factors (angiotensin II, increased sympathetic drive) often together with tissue hypoxia. The hypertrophied heart is also more prone to being electrically unstable which can predispose to arrhythmias as can ischemia and fibrosis. Hypertrophied cardiac muscle is also more sensitive to adrenergic stimulation and increased sympathetic activity is common to hypertension.

The presence of LVH negatively affects cardiac function. The predominant reason for this is myocardial fibrosis.[15] Reduced diastolic function is found early in hypertension. As fibrosis advances there is also an inability to generate myocardial force, in other words systolic function also begins to be compromised. In some cases prolonged hypertension can lead to heart failure.

**Auscultation:** Abnormal auscultatory findings are frequent in dogs and cats with hypertension. In one study 70% of hypertensive cats had abnormalities, with 40% having murmurs.[16] The presence of a murmur may not however necessarily relate to the presence of hypertension as a study in cats showed that hypertensive and normotensive cats had a similar prevalence of heart murmurs (62 vs. 72%). [17] On the other hand in this study only hypertensive cats had gallop rhythms which were present in 16% of the hypertensive cats. Gallop rhythms generally develop because of decreased left ventricular compliance secondary to ventricular hypertrophy. A new murmur or gallop rhythm should always lead to a blood pressure measurement. Other findings include tachycardia and arrhythmias.

**ECG:** Findings are not specific for hypertension and can be seen in older cats and especially in cats with heart disease or hyperthyroidism. Common findings are tall R waves (high voltage), increased heart rate and less frequently taller P-waves and dysrhythmias. Conduction abnormalities such as bundle branch blocks or left anterior fascicular block are also seen.

Fig. 3. Hypertensive dog with a prominent aorta.



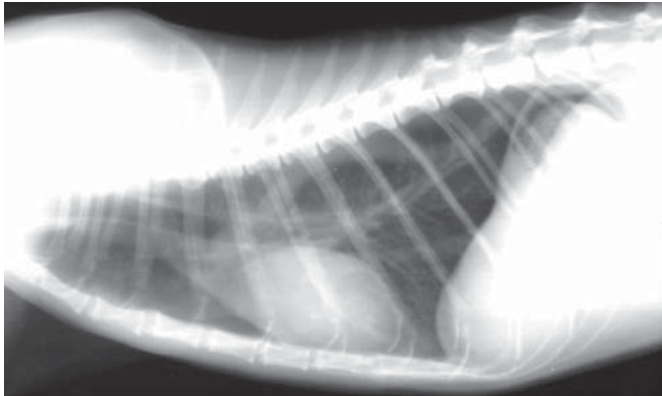


Fig. 4: Hypertensive cat with an undulating aorta.

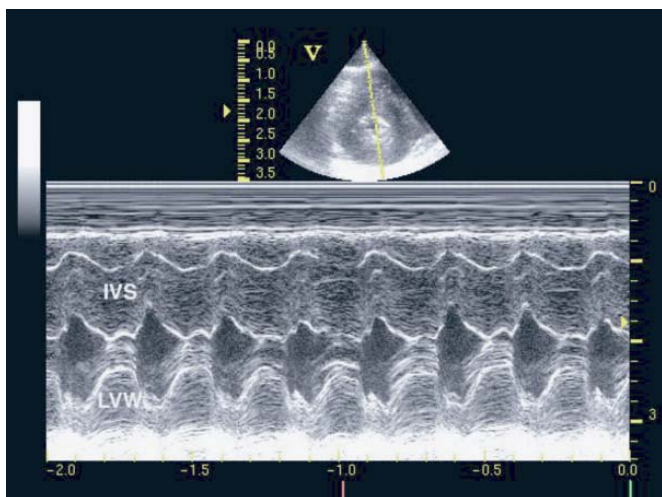
**Thoracic radiographs:** There have been limited studies addressing the radiographic findings in hypertensive patients. Some of the changes attributed to hypertension can also be seen in older patients without hypertension. In one study where normotensive older cats were compared to hypertensive cats, the only significantly different parameter was aortic undulation which was present more commonly in hypertensives.[18] Indicators of cardiomegaly were equally common in hypertensives and non-hypertensives.

#### **Echocardiography:**

Abnormal motion of the mitral valve may be seen in Echocardiography. The diastolic pattern of mitral inflow velocity recorded by pulsed wave Doppler change from normal to impaired relaxation.

In hypertensive cats left ventricular enlargement is found, often with asymmetric or symmetric thickening of the intraventricular septum and the left ventricular free wall.[17] Left ventricular internal diameter is reduced in diastole. This study shows that survival is not affected by the presence of echocardiographic changes however. Other studies have shown similar cardiac hypertrophy, however decreases in left ventricular internal

Figure 5. Echocardiogram showing marked thickening of the septum and left ventricular free wall in hypertension (Illustration above from Stepien R. Hypertension and the heart in Egner B, Carr A, Brown S: Essential Facts of Blood Pressure in Dogs and Cats. ISBN 978-3-938274-15-6, VBS GmbH 2007)



diameter were rarely found.[19], Overall the hypertrophy is in most cases relatively mild. Dilation of the proximal ascending aorta has been documented in hypertensive cats.[18] With treatment, some of the echocardiographic changes can normalize in hypertensive cats.[20]

## Treatment of Hypertension

Although a variety of medications have been suggested for treatment of hypertension in pets, ACEi and amlodipine are the predominant ones used.

#### **ACE inhibitors**

ACEi are of special interest in association with cardiac or renal disease based on the pharmacologic effects of these agents. ACEi lower intraglomerular pressure by dilating the efferent arteriole, thereby minimizing hyperfiltration. ACEi also reduce endothelial dysfunction, including of the renal vascular bed.[12] ACEi reduce proteinuria and production of cytokines that lead to fibrosis, inflammatory cell recruitment and compensatory hypertrophy.[21] When using ACEi, it is important to monitor for azotemia as this can occur secondary to the vasodilator effect. Blood pressure reduction achieved with an ACEi is usually relatively minor. ACEi as sole agents resulted in initial control of hypertension in only 6 of 16 hypertensives, after 6 months only 2 of 16 were still controlled.[22] Ramipril is an ACEi that may be more effective at controlling hypertension. A research abstract showed that in 12 hypertensive cats 0.125 mg/kg of ramipril daily resulted in good blood pressure control in all cats for up to 6 months, with an average blood pressure decline of approximately 40 mmHg.[23]

There is evidence that suggests that ACEi should be used whenever calcium channel blockers (CCBs) such as amlodipine are used to control blood pressure. CCBs dilate the afferent arteriole, resulting in increased intraglomerular pressure if systemic blood pressure is not normalized. CCBs as a sole agent were associated with increased proteinuria in humans with protein losing kidney disease unless mean arterial pressure was dramatically lowered. This was not seen if an ACEi was given concurrently.[24] A blunting of RAAS activation by amlodipine in healthy dogs was seen when enalapril was given concurrently.[25] Other ACEi's used in Europe are Benazepril (Dose rate ??) and Enalapril (Dose rate ??)

#### **Calcium Channel Blockers**

Amlodipine has been the medication that has allowed successful management of hypertension in pets, especially cats. Amlodipine decreases calcium influx into both cardiac and vascular smooth muscle leading to vasodilation. Adverse side effects from a rapid drop in blood pressure (weakness, syncope, organ failure) are rarely reported. Amlodipine (0.625 to 1.25 mg/cat/day) reduces systolic blood pressure by approximately 40 mmHg. The higher dose is usually needed in heavier cats. Transdermal amlodipine may also be efficacious in cats though higher dosages may be needed and titration to effect may be more challenging. In dogs an ideal dosage has not been determined to date. Initially 0.1 mg/kg can be given daily, this can be increased up to 0.4 mg/kg/day if needed.

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