THE IMPORTANCE OF ARTERIAL HYPERTENSION IN GERIATRIC DOGS AND ASSOCIATED DISEASES.

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Abstract
Systemic hypertension is an increasingly diagnosed disorder in dogs and cats and frequently occurs secondary to chronic kidney disease. Prevention of damage to organs such as the kidneys, brain, heart, and eyes is one of the primary concerns in the management of veterinary patients with hypertension. Hypertension can be classified as primary (essential) or secondary. Essential hypertension refers to hypertension for which the cause remains unknown after extensive diagnostic testing, whereas secondary hypertension is associated with underlying disease or administration of hypertensive agents. In contrast to humans, essential or idiopathic hypertension is rare in veterinary patients. In cats and dogs, systemic hypertension is most often associated with another disease or condition such as: Renal disease, hyperadrenocorticism, Hyperthyroidism, Pheochromocytoma, Primary hyperaldosteronism, Diabetes mellitus, Renal disease, especially chronic kidney disease (CKD), is the most common cause of hypertension in dogs; approximately 31% to 93% of dogs may be hypertensive. The Main objective of this study is to determine the importance of the detection of arterial hypertension in elderly dogs and its impact on the pathogenesis of associated diseases. Other objectives are, to determine the prevalence of hypertension in elderly dogs, the significance of the clinical manifestations of systemic hypertension and the prevalence of the most common diseases affecting geriatric dogs.
Keywords: *Arterial hypertension, Hyperadrenocorticism, Chronic kidney disease, Secondary hypertension.*

Introduction

The persistent elevation of systemic blood pressure is referred to "Systemic hypertension" (HT). Multiple end-organ systems are damaged due to chronic elevation of systemic blood pressure; some of this damage may be clinically obvious but some may be insidious. Blood pressure is discussed in terms of systolic and diastolic values. In people, when the systolic and diastolic values are elevated it is called combined HT, HT can be isolated systolic and isolated diastolic each of the three has differing morbidity and mortality rates. The importance and prevalence of isolated systolic or diastolic HT is understudied in dogs and cats, but it is clear that HT occurs in these species and is a cause of significant morbidity in some animals. Typically Systemic hypertension is classified as primary "essential" HT or secondary HT. There have been some attempts by some veterinary clinicians to distinguish essential HT from idiopathic HT which is systemic HT in the absence of overt, clinically apparent causal disease. The use of the term "idiopathic" acknowledges that there may be a causal disease like renal disease that is responsible for the HT but is still in a pre-clinical phase. The discovery of the cause of the HT is dependent on the thoroughness of the diagnostic testing especially when the underlying disease is rare like a pheochromocytoma. The majority of hypertensive dogs have developed HT as a complication of another systemic disease however some sporadic cases of essential HT in dogs have been published. The prevalence of HT varies with the population studied(Rebecca L. Stepien 2002).

There is a low prevalence HT in the general canine population but it is much higher in certain populations. Studies have shown that chronic renal disease (especially glomerular disease), hyperadrenocorticism (HAC) and diabetes mellitus (DM) are the most common diseases associated with HT in dogs.

The majority of studies report the prevalence of HT as 60–90% in dogs with chronic renal failure, and as 70–80% for dogs with HAC, Systemic HT is documented less frequently in dogs with DM with a prevalence of 25–45%. Less common conditions associated with HT in dogs include pheochromocytoma, acromegaly, primary hyperaldosteronism and use of hypertensive medications such as phenylpropanolamine. One study showed small increases in blood pressure

with increasing age in dogs, other studies found age and blood pressure were not significantly correlated. Male dogs tend to have slightly higher blood pressure readings than females but the difference is unlikely to be clinically significant. Healthy sight hounds like greyhounds, deerhounds have a higher normal range of blood pressures; normal resting blood pressure values may be up to 15 mmHg higher than other breeds of similar size. Development of HT in dogs is almost always associated with the concurrent presence of one or more identifiable underlying diseases. The search for an underlying condition responsible for the development of HT is an essential component of the diagnosis of HT in dogs (Rapoport GS 2001, Ortega TM 1996,Bodey AR 1996).

The main objective of this study is to determine the importance of the detection of arterial hypertension in elderly dogs and its impact on the pathogenesis of associated diseases.
Some other objectives are to determine the prevalence of hypertension in elderly dogs, the significance of the clinical manifestations of systemic hypertension and the prevalence of the most common diseases affecting geriatric dogs.

Physiopathology

As blood flows through the arteries it pushes against the inside of the arterial walls. The more pressure exerted on these walls, the higher the blood pressure will be. The blood pressure is also affected by the size of small arteries. The pressure of the blood flowing through relaxed muscular walls of arteries is lower than when the artery walls narrow, or constrict.

When the heart beats to push blood out into the arteries, blood pressure is at its highest. However it is at its lowest when the heart relaxes to fill with blood again. When the heart muscles contract it is called systolic pressure. When it is at rest is called diastolic pressure. The systolic pressure is stated first and the diastolic pressure second. Blood pressure is measured in millimeters of mercury.

The ABP (arterial blood pressure) is the product of cardiac output and total peripheral resistance. Cardiac output may be further factors as the product of the heart rate and stroke volume: ABP= (heart rate × stroke volume) × total peripheral resistance

Thus any factor or process that persistently elevates any of these three determinants of ABP can cause systemic hypertension (William O Reece *et al.* 2015).

Cardiac output and peripheral resistance

The balance between the cardiac output and peripheral vascular resistance is necessary to maintain a normal blood pressure. Most patients with essential hypertension have a normal cardiac output but a raised peripheral resistance. Peripheral resistance is determined by small arterioles, the walls of which contain smooth muscle cells, not by large arteries or the capillaries.

The rise in intracellular calcium concentration is thought to be related to the contraction of smooth muscle cells, which may explain the vasodilator effect of drugs that block the calcium channels. Prolonged smooth muscle constriction is thought to induce structural changes with thickening of the arteriolar vessel walls possibly mediated by Angiotensin, leading to an irreversible rise in peripheral resistance.

It has been postulated that the peripheral resistance is not raised in very early hypertension and the elevation of the blood pressure is caused by a raised cardiac output, which is related to sympathetic overactivity. The subsequent rise in peripheral arteriolar resistance might therefore develop in a compensatory manner to prevent the raised pressure being transmitted to the capillary bed where it would substantially affect cell homeostasis (William O Reece *et al.*2015).

Renin-angiotensin system

Blood pressure is mostly affected by the rennin angiotensin system where rennin gets secreted byjuxtaglomerular apparatus of the kidneyby 3 different factors: glomerular underperfusion, decreased salt intake or as a response to the sympathetic nervous system.

Angiotensinogen is converted to Angiotensin I which is rapidly converted by the angiotensin converting enzyme (ACE) to Angiotensin II in the lungs. Angiotensin II causes elevation of blood pressure through the vasoconstrictor effect that it performs and through the stimulation of the release of aldosterone from the adrenal glands that causes sodium and water retention, which in turn causes further elevation in blood pressure (William O Reece *et al.*2015).

Autonomic nervous system

Arteriolar constriction and arteriolar dilatation can be caused by the stimulation of the sympathetic nervous system. Therefore the autonomic nervous system has an important role in the maintenance of a normal blood pressure. In addition it is important in the regulation of blood pressure in response to stress and physical exercise.

Hypertension is related to an interaction between the autonomic nervous system and the renin-angiotensin system, together with other factors, including sodium, circulating volume (Guyton AC *et al.*2006).

Types of hypertension

Systemic hypertension, which is the sustained increases in BP (blood pressure), can generally be categorized into 1 of 3 types. It may be idiopathic hypertension not related to any disease, or it can be secondary hypertension which means in association with diseases that may increase blood pressure, or it can be stress-induced or white-coat hypertension.

In the absence of any identifiable predisposing causes, hypertension is described by the terms primary or essential hypertension. Animals with hypertension frequently present subclinical kidney disease which makes it difficult to establish a valid diagnosis of primary or essential hypertension. A chronic increase in BP suggests that one or both of the neurohumoral and renal systems responsible for regulating BP is abnormal. In the absence of an overt clinically apparent disease that can cause secondary hypertension then the panel recommends the use of the term idiopathic in place of essential for animals. When reliable BP measurements demonstrate a sustained increase in BP concurrent with normal CBC, serum biochemistry, and urinalysis, then a diagnosis of idiopathic hypertension is established. Unfortunately, pressure dieresis, may be induced by elevated BP and thus, the presence of low urine specific gravity (<1.030) in a patient with high BP does not establish that kidney disease is present. However, the presence of concentrated urine (>1.030) makes kidney disease less likely. Since animals with idiopathic hypertension can have underlying subclinical kidney disease or other conditions that may cause secondary hypertension, in addition to the tests listed above, according to the clinical findings, additional tests may include renal ultrasound, measurement of glomerular filtration rate, and quantitative assessment of proteinuria, and blood cortisol profile. Depending on individual cases additional tests could include serum and urine aldosterone and catecholamine concentrations and adrenal ultrasound examination. Although secondary hypertension remains the most common category of high BP in dogs, idiopathic hypertension is more common than previously recognized (Bovee*et al.*1986, Tipett*et al.*1987, Maggio *et al.* 2000, Ellliott*et al.*2001).

Secondary Hypertension

When high BP is concurrent with clinical disease or a condition known to cause hypertension like hyperadrenocorticism, hyperaldosteronism, diabetes mellitus, CKD(chronic kidney disease), obesity, hypercholesterolemia, pheochromocytoma, hypothyroidism or associated with the administration of therapeutic agents that induce an elevation of BP, such as

glucocorticoids, mineralocorticoids, erythropoietin, sodium chloride, phenylpropanolamine, and nonsteroidal anti-inflammatory drugs, this type of hypertension is known as secondary hypertension. Despite effective treatment of the primary condition hypertension may persist and the BP may increase after therapy is initiated. Even if the condition causing the secondary hypertension is effectively resolved by therapeutic intervention, prompt serial follow-up evaluations should be done (Goy-Thollot*et al.*2002,Syme*et al.*2003).

White-Coat Hypertension

As a consequence of the measurement process, artifactual increase in BP occurs, generally due to autonomic nervous system alterations from the effects of excitement or anxiety on higher centers of the central nervous system. This artifact can be reduced or eliminated by altering measurement conditions to reduce the animal's anxiety or measuring BP at the animal's home. Presently there is no justification for treating white-coat hypertension in dogs or cats. Increases in BP induced by anxiety can lead to a false diagnosis of systemic hypertension. Some animals may exhibit a dramatic increase in BP whereas others do not, and some animals may even exhibit a decrease in BP as a result of the measurement process, therefore the effects of anxiety on BP are unpredictable.The latter effect presumably is due to parasympathetic nervous system over activity (Karter*et al.*2003, Remillard RL *et al.* 1991,Hamlin RL *et al.* 1982, belew*et al.* 1999).

Measurement of blood pressure

Invasive Blood Pressure Measurement

This measurement involves arterial puncture (for acute measurement) or cannulation with use of a blood pressure monitor providing pressure tracings (figure 1). It provides a direct reflection of true intra-arterial pressure, but can be difficult for routine clinical use. The direct blood pressure monitoring is mainly used for anesthetic or acute critical care monitoring or in research situations(Stepien RL *et al.* 1999).

Fig 1. Direct blood pressure measuring technique (Stein B, 2003)

OscillometricBlood Pressure Measurement

It is a common and useful technique that benefits from the use of an automatically inflating and deflating cuff that is wrapped around a limb or tail and relies on the detection of arterial pulsation (figure 2). These techniques have been shown to accurately track variations in blood pressure over time in conscious dogs. However individual measurements obtained oscillometrically may underestimate direct systolic blood pressure measurements by up to 5–20 mmHg. Invasively measured diastolic pressure is poorly correlated to Oscillometric diastolic

pressure results in conscious dogs (Stepien RL *et al.* 1999, Bodey AR *et al.*1996, Brown S *et al.*2001, Kallet AJ *et al.* 1997).

Fig 2. Oscillometric blood pressure measurement (Amy Dixon-Jimenez et al. 2011)

Doppler methods of Blood Pressure

The Doppler method detects the arterial pulsation using piezoelectric crystals. The BP is measured using a hand inflated cuff (figure 3). This is a commonly-used and useful method of blood pressure measurement. Accuracy is dependent on user experience and meticulous attention to technique, and diastolic pressures can be difficult to discern in some animals (Sparks AH *et al.*1953, Stepien RL *et al.*1999).

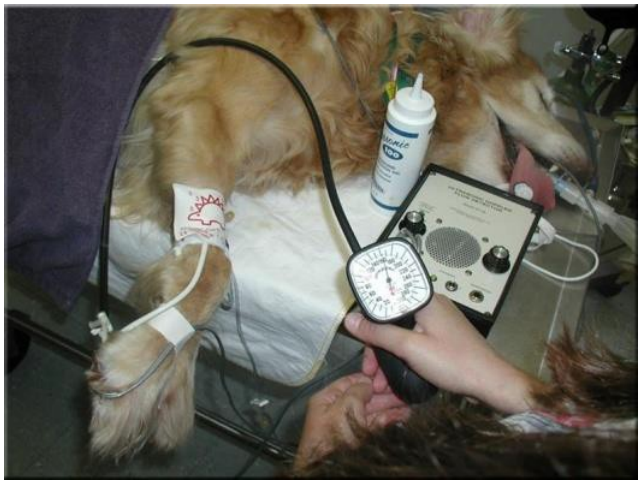

Fig 3. Doppler method general setup (Stein B, 2003)

Photoplethysmographic blood pressure measurement

This method estimates blood pressure based on attenuation of infrared radiation as a method of estimating arterial volume. Studies of its accuracy in conscious dogs and cats are not available (Brinns SH *et al.*1995).

General Measurement Recommendations

In most clinical situations the noninvasive blood pressure measurement is preferred. The American College of Veterinary Medicine Hypertension Consensus Panel 12 for acute blood pressure measurement in conscious animals includes the following:

The procedure should be performed the same way in every patient.Doppler methods are mostly used for dogs; the cuff size should be ~ 40% of circumference of limb or tail (figure 4)and always in alignment with the heart.

Several measurements should be performed, a total from 3 to 5 with 30 seconds to 1 minute interval between reading. The mean of the reading is then used (Hypertension consensus panel 2002).

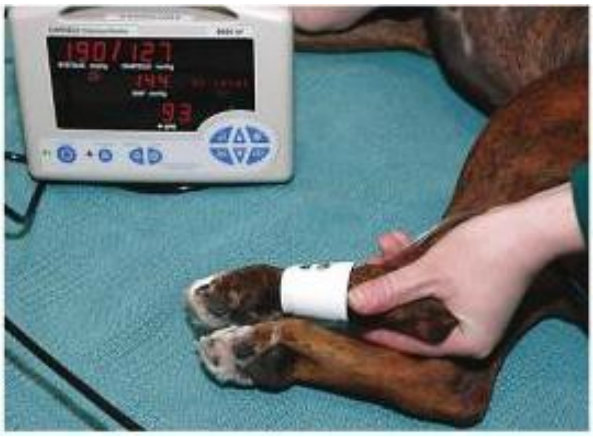

Fig 4. Demonstration of cuff placement over the cranial tibial artery in a dog (Rosemary A et al. 2016)

Patient consideration

Prior to any patient manipulation, the blood pressure should be measured to minimize the stress and have more accurate results. The owners presence to calm the animal can be beneficial.The patient should be placed in sternal or lateral recumbency, conscious and calm with no use of tranquilization to prevent interference with the results. It is recommended to keep the patient in the required position for a few minutes for batter adaptation to the procedure.

Normal values for canine blood pressure

The BP values for normal dogs have been reported in various studies (Table 1). These values vary according to several factors, including differences in subject populations, measurement techniques, and animal handling and other factors. Therefore the standardization of the technique in veterinary practice is important. In people, systolic BP and pulse pressure increases have been well-characterized. However in dogs the effects of age are less clear. Some studies have shown a small increase in BP of 1–3 mmHg/year in aging dogs. On the other hand, it has been reported that sex has an effect in dogs, with males having higher and intact females lower BP values, the difference being <10 mmHg. There are essential interbreed differences in the BP of dogs, most particularly with sighthounds (eg, Greyhounds and Deerhounds), in which BP is higher by approximately 10–20 mmHg than in mongrels. In other breeds the BP values vary by 7–10 mmHg but breed-specific ranges for normal and abnormal BP may need to be developed. Obesity is a factor for increases in BP in variety of species including dogs, an experimental study has shown a small (<5 mmHg) increase in BP was noted in obese dogs by oscillometry but not byDoppler ultrasonography (Bodey AR 1996, Mishina M 1998, Shneider HP 1964, Joles JA 1998).

Table 1

Normal canine blood pressure values (Brown S *et al.*2007)

Measurementmethod	Reference	N	Systolic	Mean	Diastolic
Intra-arterial	Anderson *et al.*	**28**	**144 ± 16**	**104 ± 13**	**81 ± 9**
	Cowgill*et al.*	**21**	**148 ± 16**	**102 ± 9**	**87 ± 8**
	Chalifoux*et al.*	**12**	**154 ± 31**	**115 ± 16**	**96 ± 12**
	Stepien*et al.*	**27**	**154 ± 20**	**107 ± 11**	**84 ± 9**
Oscillometry	Bodey and Michell	**1267**	**131 ± 20**	**97 ± 16**	**74 ± 15**
	Coulter*et al.*	**51**	**144 ± 27**	**110 ± 21**	**91 ± 20**
	Kallet*et al.*	**14**	**137 ± 15**	**102 ± 12**	**82 ± 14**
	Stepien*et al.*	**28**	**150 ± 20**	**108 ± 15**	**71 ± 18**
	Meurs*et al.*	**22**	**136 ± 16**	**101 ± 11**	**81 ± 9**
Doppler ultrasonography	Chalifoux*et al.*	**12**	**145 ± 23**		
	Stepien*et al.*	**28**	**151 ± 27**		
	Remillard*et al.*	**5**	**150 ± 16**		

Interpretation of results

The risk factor is distributed according to the systolic blood pressure and end-organ damage. If the SBP (systolic blood pressure) < 150/95, there is minimal risk, so no further diagnostics indicated.If the SBP 150/95 → 160/100, there is low risk, High blood pressure should be confirmed by several measurements. If there are no clinical signs or causative disease then search for underlying disease is recommended. Monitor over intervals of time if no disease found.

If the SBP 160/100 → 180/120, there is moderate risk.Attentive search for underlying disease should be performed. Therapy should be initiated if clinical signs are present or when rapid resolution of underlying disease is not anticipated. Monitor over time if no disease found.

If the SBP > 180/120, there is high risk.If ocular or neurologic signs are present;treat first, then proceed with diagnostic work-up for underlying disease If high risk associated disease is present; therapy is indicated.If no clinical signs and no associated diseases are present then recheck frequently: if consistently abnormal, consider therapeutic trial of antihypertensive medication (Cowgill LG *et al.*1983, Stepien RL *et al.* 1999, Kallet AJ *et al.* 1997, Remillard RL *et al.* 1991, Sparks AH *et al.*1999).

Causes of hypertension

The most commonly associated diseases with hypertension are chronic glomerular disease or tubulointerstitial diseases associated with proteinuria. When the systemic blood pressure is elevated, the kidneys initial response is to increase renal excretion of water and sodium, this mechanism acts to reduce the circulating blood volume and therefore decrease systemic hypertension. However persistent elevation in blood pressure leads to renal tubular degeneration and interstitial fibrosis, in addition glomerular hypertension results in glomerulosclerosis,

glomerular atrophy, and proliferative glomerulitis. Eventually this will lead to worsening of the hypertension and eventual renal failure(Cainet AE, Khalil RA 2002).

Several clinical signs may appear during CKD including vomiting, lethargy, diarrhea, constipation, depression, weight loss, polydipsia, anorexia, acute blindness, seizures and coma, hematuria, polyuria.

Hyperadrenocorticism

Canine hyperadrenocorticism (HAC) is a common condition seen most frequently in middle aged to older dogs. The pathophysiology of hypertension associated with hyperadrenocorticism potentially include excessive secretion of renin and activation of the renin–angiotensin system, enhanced vascular sensitivity to catecholamines (vasoconstriction) and a reduction of vasodilator prostaglandins.

It has also been postulated that hypertension in Cushing's syndrome is due to decreased renal conversion of cortisol to cortisone by the enzyme 11bHSD2, which would increase mineralocorticoid action. The high cortisol levels in Cushing's syndrome overwhelm the 11bHSD2 enzyme because of substrate saturation of mineralocorticoid receptors by cortisol. This mechanism will result in an excessive mineralocorticoid function. This excessive state will lead to hypokalemia, increased renal tubular sodium reabsorption, intravascular volume expansion, and hypertension. However, recent studies have shown that this phenomenon is not the only mechanism involved in hypertension and that glucocorticoids receptors are involved in the development of hypertension in Cushing's syndrome.

The clinical signs and physical examination findings characteristic for this syndrom include polyuria, polydipsia, polyphagia, abdominal distension, hepatomegaly and dermatologic changes such as bilaterally symmetrical alopeciaandpyoderma, urinary tract infections, diabetes mellitus, proteinuric renal disease, and pulmonary thromboembolism (Meliá*et al.* 2010,Herrtage*et al.* 2012, Goy-thollot*et al.*, Fraser *et al.*1989, Connell *et al.*1988).

Diabetes mellitus

Diabetes mellitus is a chronic disorder of carbohydrate metabolism due to relative or absolute insulin deficiency. Clinical signs of diabetes include polydipsia, polyuria, polyphagia with weight loss, bilateral cataracts, and weakness.

The pathophysiology between the occurrence of diabetes mellitus and hypertension remains unclear however some studies show that it is related to the formation of atherosclerosis.

The development of diabetes-related atherosclerosis includes the following steps: endothelial injury, smooth muscle cell proliferation, foam cell development and infiltration, platelet activation, and increased inflammation. External sources of injury to the endothelial cells and hemodynamic changes create lesions. When the endothelial permeability increases, the retention of deleterious low-density lipoproteins (LDL) will occur, these LDL will interact with the underlying extracellular matrix (ECM). This interaction will lead to the adherence of LDL to the vessel wall where it is oxidized by reactive oxygen species (ROS), which are increased during diabetes. Once oxidized, theses LDL stimulate the overlying endothelial cells to upregulate cellular adhesion molecules, chemotactic proteins, growth factors, and inhibit nitric oxide (NO) production. These factors will lead to the recruitment of monocytes and macrophages, which interact with highly oxidized aggregated LDL to form foam cells. The activated macrophages will produce Pro-inflammatory cytokines and stimulate the proliferation of vascular smooth muscle cells.ECM is produced by the Intimal smooth muscle cells which gives rise to a fibrous cap. The resulting complex plaque is unstable and prone to rupture and may lead to an acute vascular occlusion (figure 5)(Lusis AJ 2000).

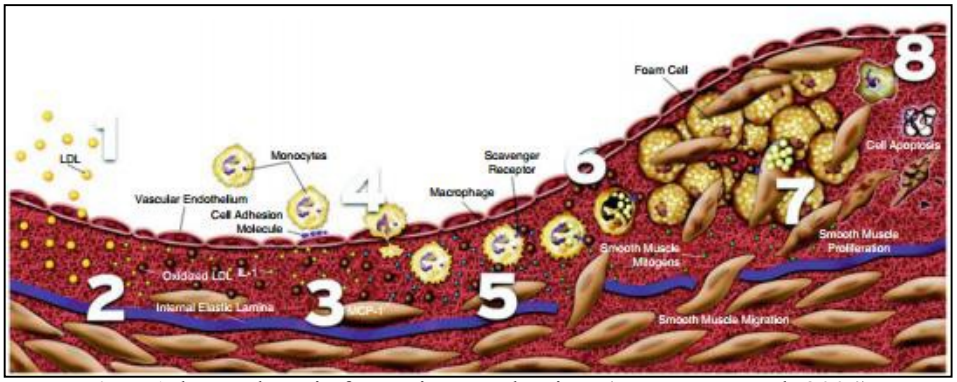

Fig 5. Atherosclerosis formation mechanism (Faxon DP et al. 2004)

Pheochromocytoma

It is a tumor of the adrenal medulla where catecholamines are excessively secreted resulting in hypertension due to several mechanisms: vasoconstriction, positive inotropic and chronotropic effect. The Clinical signs associated with this condition are often vague and intermittent, and may be similar more common diseases such as hyperadrenocortisism, diabetes mellitus, hepatic or renal disease, or other neoplasms. Clinical signs frequently observed include weakness, collapse, lethargy, anorexia, vomiting, panting, weight loss, anxiety, restlessness, polyuria, polydipsia, diarrhea, abdominal distention, epistaxis, seizures or acute blindness. The clinical signs are due to excessive secretion of catecholamine and systemic hypertension. The sudden release of catecholamines will lead to the rise of blood pressure wchich leads to precipitate acute congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation and cerebral hemorrhage(Manger *et al.*1996, Jones *et al.* 1997, Jubb*et al.* 1993, Locke-bohannon 2001).

Hyperaldosteronism

It is an excessive secretion of aldosterone by the adrenal glands. Mineralocorticoids cause an increase in blood pressure by increasing the reabsorption of sodium and therefore expanding extracellular fluid (ECF) leading to greater intravascular volume and increased arteriolar resistance.

Clinical signs include lethargy, weakness, anorexia, cervical ventroflexion, paresis, ataxia, collapse and polyuria, polydipsia along with signs indicating the presence of hypertension including hyphema, retinal detachment, hypertensive retinopathy and blindness (Weber KT 2001). However the resolution of endocrinopathy might not restore normal BP in dogs.Metabolic abnormalities such as obesity or hypercholesterolemia may result in hypertension.

Consequences and clinical signs of hypertension

Clinical signs do not appear directly with persistently elevated systemic blood pressure but this persistent elevation can lead to substantial damage to a variety of tissues and body systems over time. Essentially, the eyes, kidneys, central nervous system, and cardiovascular system are affected by persistent high ABP and they are commonly referred as the target organs of systemic hypertension.

Ocular system

The most common presenting complaint for animals with systemic hypertension is the sudden onset of blindness from hypertensive retinopathy, possibly because routine screening of animals for hypertension by ABP measurement is uncommon. As with microvascular beds, the elevation in arteriolar and capillary pressure in choroidal vessels leads to plasma leakage into vessel

walls, with resultant abnormalities including hemorrhage within retina(figure 6), vitreous, or anterior chamber, retinal detachement and atrophy, retinal edema perivasculitis, retinal vessel tortuosity and glaucoma (Smith *et al.*2016).

Fig 6.A dog with intraocular hemorrhage or hyphema causing sudden blindness (Bonagura, 2015)

Central nervous system

Head tilting, depression, seizures, which are signs consistent with cerebrovascular hemorrhage have been seen clinically in dogs with uncontrolled hypertension, and are often associated with a poor prognosis.

The brain has an autoregulation system for its circulation which generally works well. The rise in ABP causes the constriction of small arteries and arterioles which is responsible for this autoregulatory control. This phenomenon will protect the central nervous system from many of the adverse effects of systemic hypertension across a broad range of ABPs. However, these arterioles have a limited ability to prevent the transmission of elevated ABPs to the local microcirculation (arterioles, capillaries, and venules). When the ABP rises above the autoregulation limit, the pressure and the flow within the microcirculation increases, which causes an alteration in Starling forces across the capillary wall. Following the rise in intracapillary hydrostatic pressure, in particular, the transcapillary fluid filtration tends to increase, promoting the development of interstitial edema within the brain parenchyma. If the pressure rises far enough, especially if the rise is acute, local edema formation occurs and this can lead to cerebral herniation which is generally a fatal complication. The rise in intracranial pressure due to the increase in interstitial volume causes neurological dysfunction also referred to as hypertensive encephalopathy, especially because the brain is compartmentalized within the bony cranium compartment. Clinical signs caused by brain edema may include disorientation, ataxia, stupor, com and seizures.

A rapid severe rise in ABP is highly causative of hypertensive encephalopathy. The rapidity of rise of ABP affects the likelihood of development of edema, unlike with chronic hypertension (weeks to months in duration) where the arterioles are allowed to adapt, leading to an increase in the upper limit of tolerable ABP.

Medium and small arteries can be damaged and ruptured due to hypertension which results in localized ischemia (stroke) and tissue death (infarct). The animal may therefore exhibit clinical signs such as ataxia, disorientation, seizure, stupor, or coma (Smith *et al.* 2016).

Kidneys

In humans, hypertension serves as the leading cause of renal disease and frequently the latter contributes to the genesis and maintenance of systemic hypertension. In dogs it has recently been shown that systemic hypertension can contribute to renal injury in dogs with CKD.

As in other vascular beds, high pressure in renal arterioles leads to thickening of small artery and arteriolar walls by the processes of hyaline arteriosclerosis and smooth muscle hypertrophy. This process can be unevenly distributed within the renal parenchyma, resulting in interspersed areas of ischemia and hyperperfusion. Areas of ischemia may result in overproduction of rennin with resultant increases in circulating levels of angiotensin II, further raising total peripheral resistance and stroke volume, and therefore worsening systemic hypertension (Francis W K Smith *et al.* 2016).

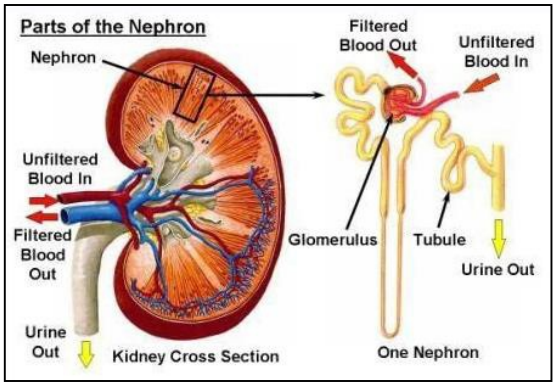

Fig 7. Blood flow through the kidney (MonisRasool, Edupil.com)

As a result to hyperperfusion in certain areas, an alteration in Starling forces in the glomerular capillary bed, with an elevation in glomerular capillary hydrostatic pressure will be initiated. When the glomerular capillary bed is injured, glomerulosclerosis(figure 7 and 8) will develop which is the production of obliterative extracellular matrix production by glomerular mesangial cells.Persistent chronic rise in hypertension can lead to nephron destruction and contribute to progression of CKD.

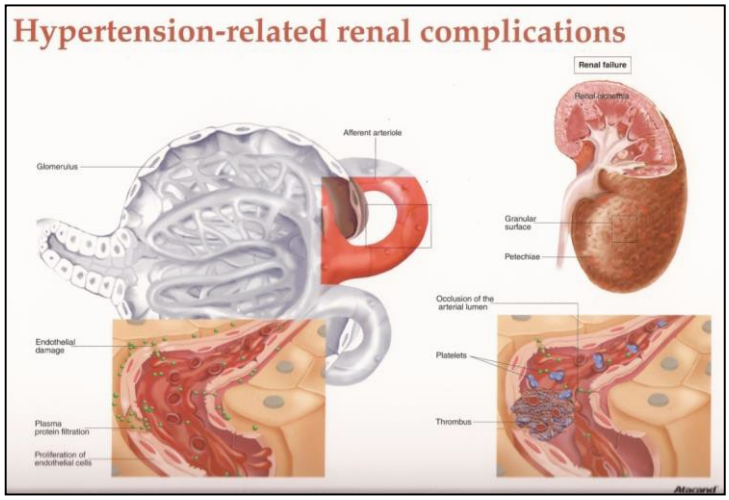

Fig 8. Formation of glomerulosclerosis (Blann, 2014)

Chronic rise in systolic BP to values > 160mmHg leads to progressive renal injury in dogs and the severity of renal injury has been correlated to the degree of elevation. Systemic hypertension can cause pathological changes in both glomerular and tubulointerstitial tissues and

can result in ischemia, necrosis, atrophy and exacerbation of proteinuria. In living animals with preexisting kidney disease, the gradual and additive changes may be difficult to quantify. However if the systolic hypertension at the time of presentation is >160mmHg, the odds of uremic crisis and the death in dogs with CKD will increase.

When there is high injury to the kidney due to hypertension, proteinuria is perhaps the best marker to demonstrate that. The presence of microalbuminuria or an elevated urine protein-to-creatinine ratio (> 0.5 in dogs) in a hypertensive animal (systolic BP > 160mmHg) should be considered an indication of ongoing renal damage (Francis W K Smith *et al.* 2016).

Cardiovascular system

Because of the increased arterial pressure (i.e., afterload), the heart will be subject to diastolic dysfunction, left ventricular hypertrophy (figure 9) and secondary valvular insufficiency.

Left ventricular hypertrophy is the most commonly observed effect of hypertension in the cardiovascular system. The hypertrophy is concentric which means increased wall thickness without luminal dilation. Left ventricular hypertrophy can cause a loss of ventricular compliance, which will result in ventricular stiffness and reduced diastolic filling that will lead to the elevation in left ventricular diastolic pressure leading to pulmonary congestion, although this effect is minor in most hypertensive dogs (Smith *et al.* 2016).

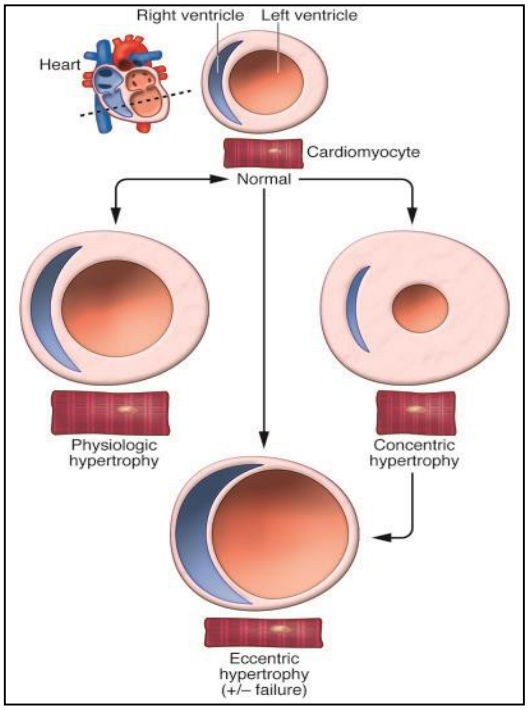

Fig 9. Different types of ventricular hypertrophy (Jop H.*et al.* 2013)

Chronic high pressure induces vascular smooth muscle hypertrophy, in small arteries and arterioles the high BP leads to extravasation of plasma into the vessel wall, producing a thickening of the vessel wall referred to as hyaline arteriosclerosis(figure 10)(Francis W K Smith *et al.*2016).

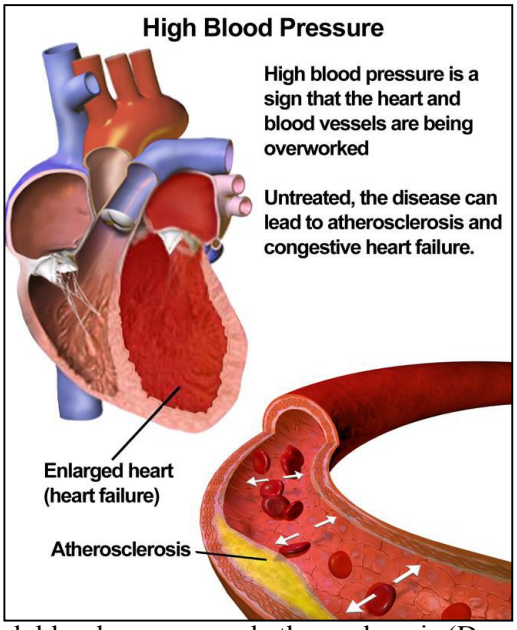

Fig 10. High blood pressure and atherosclerosis (Duggan 2008)

When these two processes occur in systemic arterioles there will be a reduction in luminal diameter producing local ischemia or generalized increase in total peripheral vascular resistance. This will in turn exacerbate the systemic hypertension, an example of deleterious positive feedback loop and may contribute to vascular rupture (stroke) in the central nervous system.

Table 2

Evidence of target organ damage (Brown S *et al.* 2007)

Tissue	**Hypertensiveinjury (TOD)**	**Clinical findings indicative of TOD**	**Diagnostic test (s)**
Kidney	Progression of chronic kidney disease	Serial increases in serum creatinine or decrease in glomerular filtration rate	Serum creatinine and urea Urinalysis with quantitative assessement of proteinuria and albuminuria GFR measurement
Eye	Retinopathy/choroidopathy	Acute onset blindness Retinal hemorrhage/edema Vitreal hemorrhage Hyphema Secondary glaucoma	Ophthalmic evaluation including a funduscopic examination
Brain	Encephalopathy Stroke	Centrallylocalizingneurologicalsigns	Neurologicalexam Magneticresonance
Heart and vessels	Left ventricular hypertrophy Cardiac failure	Left ventricular hypertrophy Gallop rhythm Arrhythmia Systolicmurmur	Auscultation Thoracic radiography Cardiac ultrasound Electrocardiogram

Diagnosis of Hypertension and associated diseases

In the diagnosis of hypertension it is essential to recognize conditions that may be factors to increased BP, to determine the extent of TOD(target organ damage) (table 2), and to search if there are any seemingly unrelated concurrent conditions that may complicate antihypertensive therapy. The discovery of underlying diseases that may cause secondary hypertension should be identified and treated while continuing to monitor BP.

A diagnosis cannot be made on the basis of a single measurement session, but on the basis of several measurements, as well as a thorough search for TOD (and conditions that may cause secondary hypertension) (figure 11 and 12). However when there is evidence of TOD consistent with hypertension such as hypertensive retinopathy/choroidopathy or encephalopathy, a single measurement of BP can be used to establish temporarily a rationale for antihypertensive therapy. Marked systemic hypertension and TOD have a solid association in dogs and cats, particularly for ocular and renal injury. But there are other adverse effects of systemic hypertension that are theorized on the basis of extrapolation from clinical studies in humans or from experimental studies in laboratory rodents (Bodey AR *et al.* 1996, Cox RH *et al.*1976).

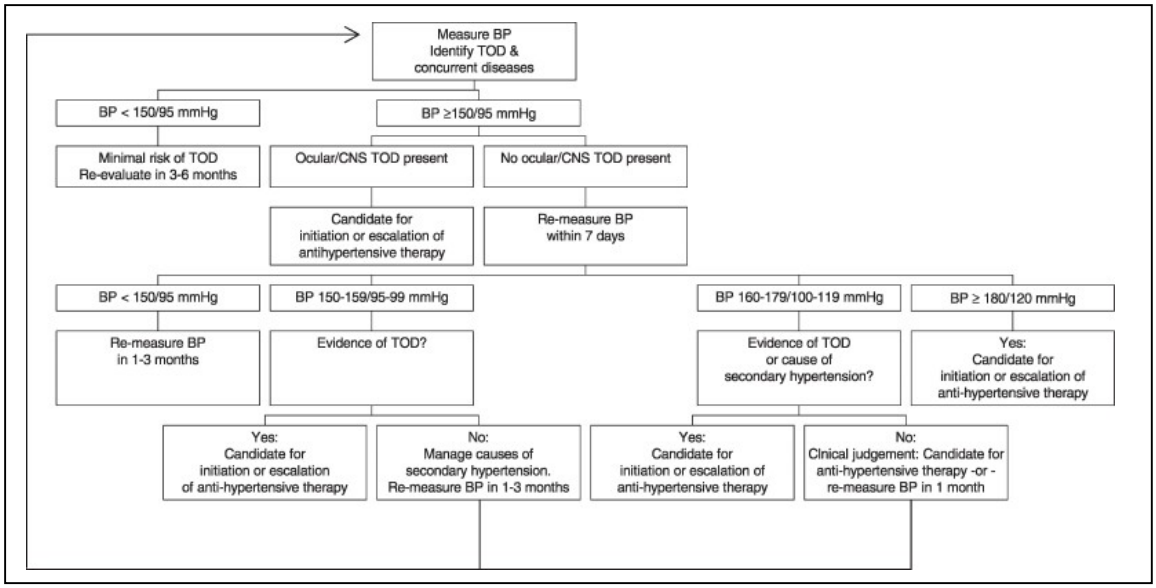

Fig 11. The recommended approach to patient evaluation (Brown S et al. 2007)

The biochemistry panel is a series of tests performed on serum, in this study the tests included BUN (Blood Urea Nitrogen), creatinine, cholesterol, glucose, SGPT (serum glutamic pyruvic transaminase), ALP (Alkaline phosphatase).

These tests provide information about the activity of the organs in the body and help detect any abnormalities.

The purpose of each test performed is detailed below.

Urea level increases in case of high dietary proteins, poor quality dietary protein, carbohydrate deficiency, catabolic states, dehydration, congestive heart failure, renal failure, blocked urethra, and ruptured bladder. It decreases in case of low dietary protein, gross sepsis, anabolic hormonal effects, liver failure, portosystemic shunts (congenital or acquired). This test is indicated in case of renal disease which is the main interest of this test in our study (Whitebread, 2015).

Creatinine level increases in case of renal malfunction, blocked urethra, and ruptured bladder. It decreases in case of sample deterioration. This test is used especially for the detection of renal disease which the reason this test was performed in this study (Whitebread, 2015).

SGPT (serum glutamic-pyruvic transaminase) is a liver enzyme is present in the cytoplasm and mitochondria of hepatocytes and, therefore, increases in case of hepatocellular damage. It is interesting to perform this test in this study to detect liver damage that can cause hypertension like liver cirrhosis, however it is not specific (Whitebread, 2015).

ALP (alkaline phophatase) level rises when there is an increased bone deposition, liver damage, cholestasis, intestinal damage, corticosteroid administration, barbiturate administration, generalized tissue damage (including neoplasia). The level also rises in hyperadrenocorticism and hyperthyroidism which are the main interest of this test in our study because they are common causes of hypertension in dogs (Whitebread, 2015).

Glucose level increases after high-carbohydrate meals, sprint exercise, due to stress or excitement, glucocorticoid administration, overinfusion with glucose/dextrose-containing IV fluids. Increases in glucose levels in the blood are evident in diabetes mellitus and hyperadrenocorticism which are the reason for performing this test in this study because they induce hypertension. Glycemia decreases in case of insulin overdose, insulinoma, acute febrile illness, and idiopathically(Whitebread, 2015).

Cholesterol level rises after ingestion of fatty meals, due to hepatic or biliary disease, protein-losing nephropathy, diabetes mellitus, hyperadrenocorticism, and hypothyroidism, the last three diseases stated are the reason for performing this test in this study because they are common conditions for the occurrence of hypertension. Cholesterolemia decreases in some cases of severe liver dysfunction and occasionally in hyperthyroidism (Whitebread, 2015).

A ***CBC*** (complete blood count) gives information on the hydration status, anemia (CKD, atherosclerosis), infection, the blood's clotting ability, and the ability of the immune system to respond. For example in cushing disease leukocytosis and thrombocytosis can be present with the manifestation of the stress formula which is neutrophilia and lymphopenia(corticosteroids have direct cytotoxic action on lymphocytes), eaosinopenia(medullary sequestration of eosinophils) and monocytosis(Deborah S. Greco 2003). In diabetes a neutrophilia can be present but it is neither specific nor systematic.

In pheochromocytoma, the CBC may reveal anemia (from chronic disease or blood loss) or a transient thrombocytopenia if the patient has platelet consumption from episodic hemorrhage. The leukogram often reveals leukocytosis characterized by a mature neutrophilia due to either catecholamine induced by demargination of neutrophils or necrosis/inflammation within the tumor(Locke-Bohannon and Mauldin; 2001).

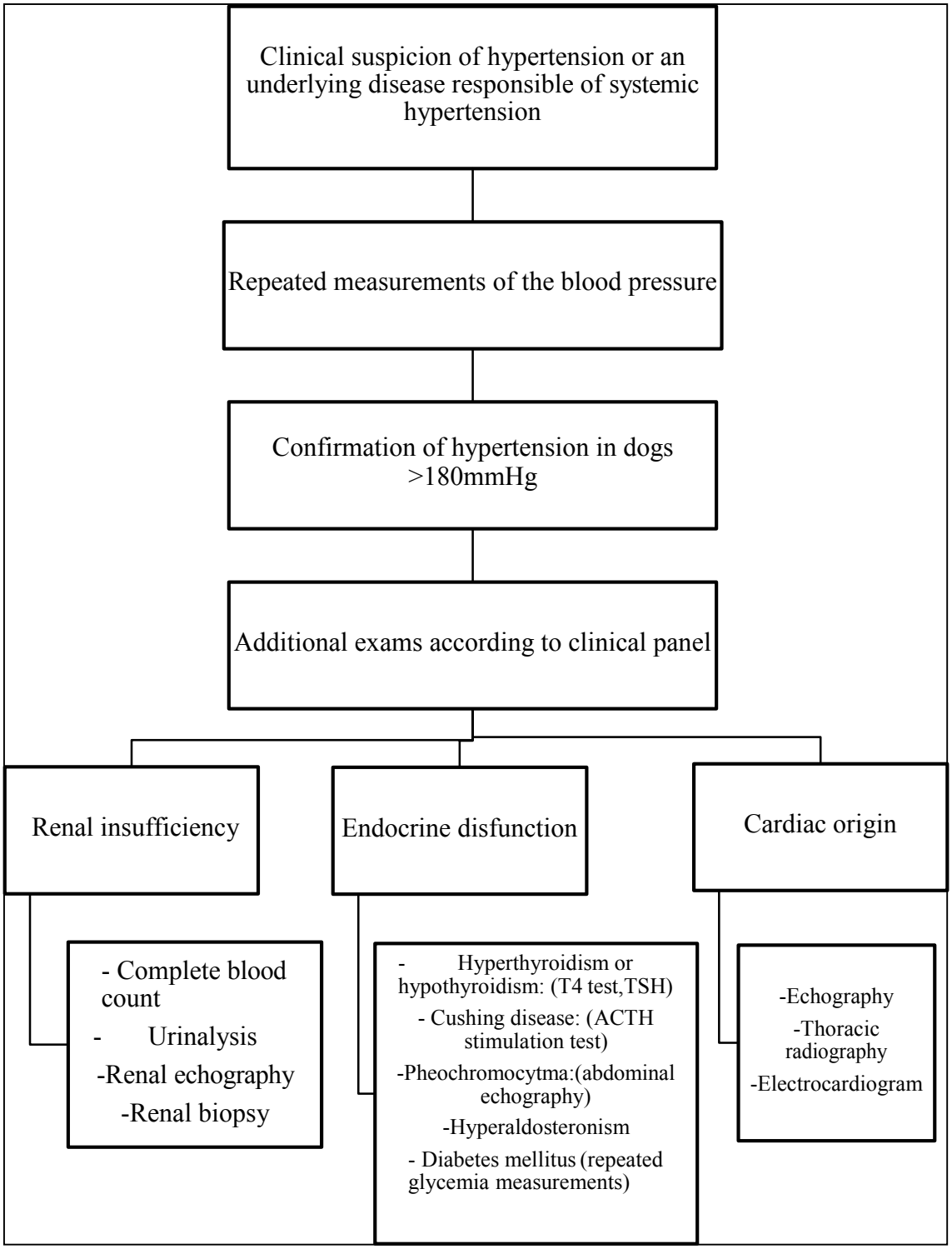

Fig 12.Diagnosis procedure of hypertension (Author, 2016

Treatment guidelines

When systolic BP is sustained at >200mmHg or diastolic BP at >120mmHg, antihypertensive treatment should be indicated regardless of other clinical findings.

Table 3

Blood pressure staging (Author, 2016)

Risk of Future Target Organ Damage(Risk levels AP0-AP3)

	(AP0)	(AP1)	(AP2)	(AP3)
Blood pressure (mm Hg)				
Systolic	<150	150-159	160-179	≥180
Diastolic	<95	95-99	100-119	≥120
Substage				
No complications present (nc)†	AP0nc	AP1nc	AP2nc	AP3nc
Complications present (c)	AP0c	AP1c	AP2c	AP3c
Should patient be treated?				
No complications present†	No	No	±	Yes
Complications present	No	Yes	Yes	Yes

- * If blood pressure is not measured, the patientis classified as risk not determined.
- I complications include any evidence of target organ damage in eyes (intraocular hemorrhage or retinal detachment), central nervous system (seizures or otherwise unexplained neurologic signs), cardovascular system (congestive heart failure), or kidneys (azotemia or proteinuria)

The patient is considered a candidate for antihypertensive therapy when there is clear evidence of ongoing TOD.

BP measurement in dogs presents considerable uncertainty and difficulty. Thus, according to table 3 when the BP is classified as AP2nc (no clinical abnormalities related to systemic hypertension are identified), the rationale for therapy is less clear(table 3). There is a difference of opinion between clinicians whether there is or not a need for treatment at this stage. Animals with no clinical signs and mildly elevated BP (AP1nc) should not be treated.

Mostly in dogs the hypertension is secondary in dogs therefore antihypertensive drug therapy by itself is often not sufficient. It is important to identify and manage conditions likely to be causing secondary hypertension and to determine the extent of TOD (Kobayashi DL *et al.*1990, Ortega TM *et al.* 1996, Jacob F *et al.*2003).

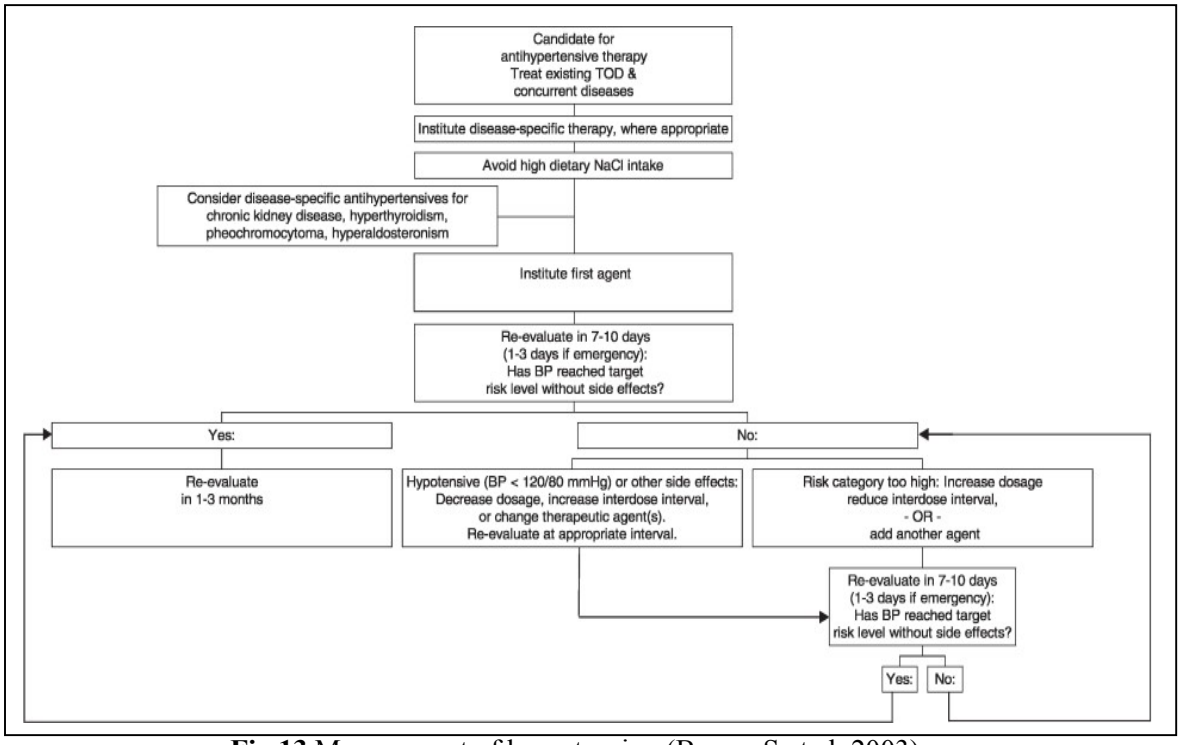

Fig 13. Management of hypertension (Brown S et al. 2003)

Conditions that cause secondary hypertension should be effectively managed to completely or partially resolve high BP. In order to start antihypertensive therapy, all clinically available information should be integrated and once the decision is made periodic re-evaluation is mandatory (figure 13). The therapy must be tailored to the patient and its associated conditions. The fewer the treatments the more preferable, once-daily treatment is ideal. Acute and abrupt decreases in BP should be avoided; a gradual, sustained reduction is the therapeutic goal.. In veterinary patients, the management of hypertension usually requires more than one agent, if the agent used is partially effective, an increase in the dosage or the addition of a new agent is considered. Dietary salt restriction is controversial in the management of high BP, there are evidence that suggest that sodium restriction alone does not decrease BP. On the contrary, in some cases sodium restriction activates the renin-angiotensin-aldosterone axis and may actually increase BP and therefore cause vascular, renal, and cardiac changes which will necessitate the utilization of antihypertensive agents that interfere with this hormonal system for example angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and aldosterone receptor blockers. On the other hand in animals with CKD, high salt intake may produce adverse consequences. Hypertension is managed in a stepwise manner by a staged institution of dietary and pharmacological regimens, taking into consideration all concurrent diseases and the extent of TOD. It is essential to evaluate the patient repeatedly, and adjust the treatment according to the evolution of the course of the diseases and the extent of TOD (Mathur S *et al.* 2002, Grauer G *et al.* 2000, Brown SA *et al.* 2003, Brown SA *et al.* 1993, Gaber L *et al.* 1994).

Once a decision is made to treat an animal with hypertension, diet adjustment and therapeutic intervention with pharmacological agents is carried out. The selection of appropriate diet should be based on other patient-specific factors, such as underlying or concurrent diseases and palatability. Each case should be thoroughly studied because each condition is best treated with

specific classes of agents, such as the use of beta-blockers for hypertension associated with hyperthyroidism. In the case of pheochromocytomas, alpha- and betablockers are used or surgical excision is performed. In animals suffering from hypertension associated to hyperaldosteronism, aldosterone receptor blockers or surgical excision of adrenal tumors are the best choices. As for dogs with CKD some combination of ACEI, ARB, and aldosterone receptor blockers are used. ACEI and calcium channel blockers (CCB) are the most widely used antihypertensive agents in veterinary medicine (King GL *et al.*2006, Brown SA *et al.* 2001, Brown SA *et al.* 2003, Brewster UC *et al.* 2003, Atkins CE *et al.* 2002).

References

1. Rapoport GS, Stepien RL. Direct arterial blood pressure measurement in 54 dogs presented for systemic hypertension screening 1998-2001 (abstract). 11thCongress, European Society of Veterinary Internal Medicine 2001;62.
2. Remillard RL, Ross JN, Eddy JB.Variance of indirect blood pressure measurements and prevalence of hypertension in clinically normal dogs.Am J Vet Res 1991;52:561-565.
3. Syme HM, Barber PJ, Markwell PJ, Elliott J. Prevalence of systolic hypertension in cats with chronic renal failure at initial evaluation. J Am Vet Med Assoc 2002;220:1799-1804.
4. Maggio F, DeFrancesco TC, Atkins CE, *et al.*Ocular lesions associated with systemic hypertension in cats: 69 cases (1985- 1998). J Am Vet Med Assoc 2000;217:695-702.
5. Littman MP, Robertson JL, Bovee KC. Spontaneous systemic hypertension in dogs: Five cases (1981-1983). J Am Vet Med Assoc 1988;193:486-494.
6. Tippet TE, Padgett GA, Eyster G, *et al.*Primary hypertension in a colony of dogs. Hypertension 1987;9:49-58.
7. Stiles J, Polzin DJ, Bistner SI. The prevalence of retinopathy in cats with systemic hypertension and chronic renal failure or hyperthyroidism. J Am AnimHospAssoc 1994;30:564-572.
8. Kobayashi DL, Peterson ME, Graves TK, *et al.*Hypertension in cats with chronic renal failure or hyperthyroidism. J Vet Intern Med 1990;4:58-62.
9. Sparkes AH, Caney SMA, King MCA, Grufydd-Jones TJ. Inter- and intraindividual variation in Doppler ultrasonic indirect blood pressure measurements in healthy cats. J Vet Intern Med 1999;13:314-318.
10. McCubbin JW, Corcoran AC. Arterial pressures in street dogs: Incidence and significance of hypertension. ProcSocExpBiol Med 1953;84:130-131.
11. Bodey AR, Michell AR. Epidemiological study of blood pressure in domestic dogs.J SmAnimPract 1996;37:116-125.
12. Struble AL, Feldman EC, Nelson RW, Kass PH. Systemic hypertension and proteinuria in dogs with diabetes mellitus. J Am Vet Med Assoc 1998;213:822-825.
13. Ortega TM, Feldman EC, Nelson RW, *et al.*Systemic arterial blood pressure and urine protein/creatinine ratio in dogs with hyperadrenocorticism. J Am Vet Med Assoc 1996;209:1724-1729.
14. Stepien RL, Rapoport GS.Clinical comparison of three methods to measure blood pressure in nonsedated dogs. J Am Vet Med Assoc 1999;215:1623-1628.
15. Schneider HP, Truex RC, Knowles JO. Comparative observations of the hearts of mongrel and greyhound dogs.Anat Rec 1964;149:173-180.
16. Anderson LJ, Fisher EW.The blood pressure in canine interstitial nephritis.Res Vet Sci 1968;9:304-313.
17. Cowgill LG, Kallet AJ. Recognition and management of hypertension in the dog In: Kirk, RW and Bonagura, JD, eds. Current Veterinary Therapy VIII: Small Animal Practice. Philadelphia: W.B. Saunders Company 1983;1025-1028.
18. Maggio F, DeFrancesco TC, Atkins CE, *et al.*Ocular lesions associated with systemic hypertension in cats: 69 cases (1985-1998). J Am Vet Med Assoc 2000;217:695–702.
19. 19.Elliott J, Barber PJ, Syme HM, *et al.* Feline hypertension: Clinical findings and response to antihypertensive treatment in 30 cases. J Small AnimPract 2001;42:122–129.
20. Goy-Thollot I, Pechereau D, Keroack S, *et al.*Investigation of the role of aldosterone in hypertension associated with spontaneous pituitary-dependent hyperadrenocorticism in dogs. J Small AnimPract 2002;43:489–492.

21. Syme HM, Elliott J. Prevalence of hypertension in hyperthyroid cats at diagnosis and following treatment. J Vet Int Med 2003;17:754A.
22. Karter Y, Curgunlu A, Altinisik S, *et al*. Target organ damage and changes in arterial compliance in white coat hypertension. Is white coat innocent? Blood Press 2003;12:307–313.
23. Kallet AJ, Cowgill LD, Kass PH. Comparison of blood pressure measurements obtained in dogs by use of indirect oscillometry in a veterinary clinic versus at home. J Am Vet Med Assoc 1997;210:651–654.
24. Belew AM, Barlett T, Brown SA. Evaluation of the whitecoat effect in cats. J Vet Intern Med 1999;13:134–142.
25. Mathur S, Syme H, Brown CA, *et al.* Effects of the calcium channel antagonist amlodipine in cats with surgically induced hypertensive renal insufficiency. Am J Vet Res 2002;63:833–839.
26. Branson KR, Wagner-Mann CC, Mann FA.Evaluation of an oscillometric blood pressure monitor on anesthetized cats and the effect of cuff placement and fur on accuracy. Vet Surg 1997;26: 347–353.
27. Bodey AR,Michell AR. Longitudinal studies of reproducibility and variability of indirect (oscillometric) blood pressure measurements in dogs: Evidence for tracking. Res Vet Sci 1997;63:15–21.
28. Brown SA, Haberman C, Morgan J. Evaluation of Doppler ultrasonographic and oscillometric estimates of blood pressure in conscious dogs. J Vet Int Med 2001;15:307
29. Caulkett NA, Cantwell SL, Houston DM.A comparison of indirect blood pressure monitoring techniques in the anesthetized cat. Vet Surg 1998;27:370–377.
30. Brown SA, Haberman C, Morgan J. Evaluation of Doppler ultrasonographic and oscillometric estimates of blood pressure in cats. J Vet Int Med 2001;15:281 (abstract).
31. Truett AA, West DB. Validation of a radiotelemetry system for continuous blood pressure and heart rate monitoring in dogs.Lab AnimSci 1995;45:299–302.
32. Brown CA, Munday J, Mathur S, Brown SA. Hypertensive encephalopathy in cats with reduced renal function. VetPathol. 2005;42:642–649.
33. Pettersen JC, Linartz RR, Hamlin RL, *et al*... Noninvasive measurement of systemic arterial blood pressure in the conscious beagle dog.Fundamental and Applied Toxicology 1988;10:89–97.
34. Bodey AR, Michell AR. Epidemiological study of blood pressure in domestic dogs.J Small AnimPract 1996;37:116–125.
35. Bright JM, Dentino M. Indirect arterial blood pressure measurement in nonsedated Irish wolfhounds: Reference values for the breed. J Am AnimHospAssoc 2002;38:521–526.
36. Dukes' Physiology of Domestic Animals edited by William O. Reece, Howard H. Erickson, Jesse P. Goff, Etsuro E. Uemura.
37. Manual of Canine and Feline Cardiology By Francis W. K. Smith Jr., Larry P. Tilley, Mark Oyama, Meg M. Sleeper.
38. Hypertension in Cats and Dogs Rebecca L. Stepien, DVM, MS, Diplomate ACVIM (Cardiology) University of Wisconsin.
39. Guidelines for the Identification, Evaluation, and Management of Systemic Hypertension in Dogs and Cats S. Brown, C. Atkins, R. Bagley, A. Carr, L. Cowgill, M. Davidson, B. Egner, J. Elliott, R. Henik, M. Labato, M. Littman, D. Polzin, L. Ross, P. Snyder, and R. Stepien.
40. Melián C, M. Pérez-Alenza, D, Peterson ME. Hyperadrenocorticism in dogs, In: Ettinger SJ (ed): Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat (Seventh Edition). Philadelphia, Saunders Elsevier, 2010;1816-1840.
41. Herrtage ME, Ramsey IK. Canine hyperadrenocorticism. In: Mooney CT, Peterson ME, eds. BSAVA Manual of Canine and Feline Endocrinology. 4th ed. Quedgeley, Gloucester: British Small Animal Veterinary Association; 2012:167-189.
42. Goy-Thollot I, Pechereau D, Keroack S, *et al*... Investigation of the role of aldosterone in hypertension associated with spontaneous pituitary-dependent hyperadrenocorticism in dogs. Journal of Small Animal Practice 2002;43:489–492.
43. Fraser R, Davies DL, Connell JM. Hormones and hypertension. ClinEndocrinol. 1989;31:701–46.[PubMed]
44. Connell JM, Whitworth JA, Davies DL, Richards AM, Fraser R. Hemodynamic, hormonal, and renal effects of adrenocorticotrophic hormone in sodium-restricted man. J Hypertens. 1988;6:17–23. [PubMed]
45. Manger W, Gifford RW. Clinical and Experimental Pheochromocytoma. Second Edition Blackwell Science; Cambridge: 1996.Jones TC, BD Hunt and NW King: 1997. Veterinary Pathology. Baltimore: Williams and Wilkens.

46. Jubb KVF, PC Kennedy, N Palmer (Eds): 1993. Pathology of Domestic Animals, 4th ed. San Diego: Academic Press, 1993.
47. Locke-Bohannon LG and GE Mauldin: 2001. Canine Pheochromocytoma: diagnosis and management. Compendium on Continuing Education for the Practicing Veterinarian 23: 807-814.
48. CainetAE, Khalil RA 2002 Pathophysiology of essential hypertension: Role of the pump, the vessel and the kidney. *SeminNephrol* 22(1):3-16.
49. Faxon DP, Fuster V, Libby P. Atherosclerotic vascular disease conference: Writing Group III: Pathophysiology. Circulation. 2004;109(21):2617–25. With permission from Lippincott Williams & Wilkins.
50. Weber KT. Mechanisms of disease: Aldosterone in congestive heart failure. NEngl J Med 345:1689-1700, 2001.
51. Locke-Bohannon LG and GE Mauldin: 2001. Canine Pheochromocytoma: diagnosis and management. Compendium on Continuing Education for the Practicing Veterinarian 23: 807-814.
52. LusisAJ .Atherosclerosis.Nature. 2000;407(6801): 233–41.
53. Duggan 2008, BetterHealth 2010.http://www.bohone2010.wikispaces.com/Group+4
54. Blann 2004 https://www.emaze.com/@ACLLTLCT/NRSG-353-IBL-Team-e-Poster-
55. Bonagura 2015,http://www.petplace.com/article/dogs/diseases-conditions-of-dogs/heart-blood-vessels/hypertension-in-dogs.
56. Deborah S Greco,DVM, PhD,DACVIM Merck vet manual 2003.
57. Stein B 2003, http://www.vasg.org/doppler_use.htm.
58. Rosemary a *et al.* 2016 http://veteriankey.com/systemic-hypertension-2.