

Blood pressure regulation and mechanism of hypertension development in dogs and cats: A review

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ABSTRACT: The review article aims at discussing the mechanisms of blood pressure regulation and hypertension development in dogs and cats. This will enhance the knowledge of clinicians and researchers on the pathophysiology of hypertension and mechanisms of normal blood pressure regulation in small animals. Hypertension is a risk factor for other cardiovascular diseases in man and animals, however, most small animal clinicians do not routinely check the blood pressure until the animals are presented with complications. Hypertension in animals can be essential or secondary but the secondary type is predominant. Blood pressure is regulated by vasoactive agents and hormones such as nitric oxide, bradykinin, endothelin-1, angiotensin II and aldosterone. The blood vessels and the kidney also play major roles in blood pressure regulation. Alterations in the regulation frameworks result in hypertension and cardiovascular diseases as elucidated in this review article. It is therefore essential that the body maintain good anatomic, physiologic and biochemical functions to maintain blood pressure. In conclusion, adequate knowledge of the mechanism by which blood pressure is regulated and the pathophysiology of hypertension will enhance research and potentiate the management of cardiovascular diseases and associated disorders in small animals.

Keywords: Blood pressure, dogs, endocrine disorder, hypertension, vasoactive agents.

INTRODUCTION

A persistent elevation of blood pressure is known as hypertension. The pulsing of blood against the walls of vessels is known as pulse. All parts of the body are supplied with blood through supply pathways. High blood pressure has been defined as systolic OR diastolic pressure in excess of or equal to 140/90 mmHg in the most recent Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure report (Atefi *et al.*, 2021). When it comes to blood pressure, 120/80 mmHg is considered normal in men and rats, and the newly introduced class of pre-hypertension is reserved for blood pressures between these two values.

Tissues and organs need the oxygenated blood that the circulatory system distributes throughout the body in order to function properly. Blood flows via a network of blood vessels that include the aorta, veins, and arteries

whenever the heart beats (Lombardi *et al.*, 2018). The resulting pulse of tension is the result of two forces: in the process of heart contraction to pump out blood into the systemic blood circulation, the main force (systolic blood pressure) is created. When the heart rests between beats, the subsequent power (diastolic blood pressure) is generated.

The amount of blood the heart syphons and the vascular resistance against the blood flow are both factors in reducing blood pressure. Hypertension is more severe with increasing cardiac output and the narrowing of the blood vessels. Canine and feline systolic blood pressures typically range between 120 and 130 millimetres of mercury. In emergency clinics, a high systolic blood pressure compensation of up to 160 mmHg is often used since many of our patients are restless (referred to as

"white coat impact"). Pets may suffer from hypertension or primary hypertension in the same way that humans do (Fang, 2021). Congestive heart failure is a possible complication of hypertension in dogs. Chronic renal disease, vision impairment as a consequence of retinal degeneration. Cat hypertension has been shown to respond well to treatments that address the underlying causes of kidney failure and hyperthyroidism (AlMarabeh *et al.*, 2019).

Therefore, the objective of this study is to discuss the mechanisms of blood pressure regulation and hypertension development in dogs and cats.

HYPERTENSION

Causes of hypertension

Most animal cases and approximately one in every twenty human cases of hypertension are caused by existing medical conditions or the use of a particular drug (Tian and Liang, 2021). There are a number of medical conditions that may lead to high blood pressure, including renal disease, diabetes, and sleep apnoea, obstructing the flow of air into and out of the body, glomerulonephritis, Cushing's disorder, acromegaly, hyperaldosteronism, and lupus - a condition in which the immune system attacks parts of the body, resulting in a variety of symptoms (Tian and Liang, 2021). Scleroderma, problems with organs and veins, may also cause hypertension (Atefi *et al.*, 2021).

In dogs, secondary hypertension, or hypertension caused by underlying sickness, is a common occurrence. Chronic kidney infection, Cushing's disease and growths in the adrenal glands are the most well-known canine illnesses that may cause hypertension. Canine hypertension affects as much as 10% of the canine population. The most common cause of hypertension in cats and dogs is kidney disease, especially chronic kidney disease (CKD) (Kiuchi *et al.*, 2019). Approximately 20 to 60% of felines and 31 to 93% of dogs with renal infection might be hypertensive (Kiuchi *et al.*, 2019).

Even though the adverse effects of hypertension are usually undetectable, a common symptom in dogs is the gradual or sudden onset of vision impairment due to vein rupture in the retina. In order to effectively treat hypertension, one must first identify and treat the underlying ailment. Hypertension in animals often goes away after a course of medication (Claassen, 2021). Hypertension may be managed with the use of medications such as angiotensin-converting enzyme inhibitors, calcium channel blockers, and vasodilators. Cat hypertension has been linked to kidney failure and hyperthyroidism, which are the two of the most common causes. Hypertension may be caused by a variety of conditions, including heart infections (Kobayashi *et al.*, 1990).

The most well-known clinical findings in cat hypertension are visual abnormalities. Among these are pupillary dilation in which pupils do not close when exposed to light, blood accumulating in the eyes, and problems with vision (Hall *et al.*, 2019). Hypertension in the eye causes the retina to detach, resulting in visual impairment. When a cat keeps running into things that are in its path, it is more likely to develop visual impairment. Heart murmur or liver or kidney-related clinical symptoms including increased water intake or urine, vomiting, and weight loss may be connected with hypertension (Ding and Zhang, 2019). There are a variety of symptoms that might indicate a seizure, including convulsions and recumbence with nasal discharges.

Types of hypertension (HBP)

Primary hypertension

The blood pressure rises for no apparent cause, the affected human or animal may be suffering from essential hypertension (also known as basic hypertension). In the medical community, it is referred to as idiopathic or basic hypertension or just hypertension. Blood pressure that exceeds the normal range (80-120/60-80 mmHg for men and 110-160/60-90 mmHg in dogs and cats) is considered abnormal (Iturriaga and Castillo-Galán, 2019). As a result, the internal stress levels of the affected man or animal are likely to be greater than they should be. Essential hypertension damages the blood vessels, causing them to become enlarged (Iturriaga and Castillo-Galán, 2019). Over time, the condition deteriorates and may lead to a wide range of serious health issues, including; cerebrum aneurysms, Alzheimer's, heart disease, renal disease, paralysis, stroke, and eyesight loss in dogs and cats as well as in men.

Secondary hypertension

Having high blood pressure as a side effect of having another health problem is called secondary hypertension (optional hypertension). The kidneys, arteries, heart, and endocrine framework may all cause optional hypertension. Pregnancy-related secondary hypertension is also possible (Hall *et al.*, 2019). The risk of serious complications, such as cardiovascular disease, renal failure, and stroke, may be reduced if secondary hypertension is managed well, which is often the case.

White coat hypertension

Some people and animals have high blood pressure when they are in the hospital environment but at the home and

natural environment, the blood pressure returns to normal. This type of hypertension is known as white coat hypertension (Bishop *et al.*, 2021). White coats are worn by experts and clinical professionals from time to time, giving the disease its name (Bishop *et al.*, 2021). A good blood pressure reading is between 120 and 80 millimetres of mercury. Having a blood pressure of more than 140/90 is considered hypertension. An animal's blood pressure may be elevated due to white coat condition, which is not always a minor problem of doctor-related anxiety (Coleman and Brown, 2020). A disease known as white coat disorder in certain animals may be a sign of a more serious circulation problem.

Causes of primary/idiopathic hypertension

Primary hypertension is also called idiopathic hypertension because the causes are mostly unknown. However, some factors have been identified to predispose to primary hypertension. These include basic circumstances such as insidious tendencies that put one at risk for developing basic essential hypertension including age, being a seasoned creature, a salt-heavy diet, a family history of hypertension, obesity, a sedentary lifestyle with little physical activity, and sleep problems, comparable to insomnia (Saxton, 2019). Although these habits mostly relate to the lifestyles of human beings, it does not make them any less of a risk factor for animals like cats and dogs (Saxton, 2019).

Causes of secondary hypertension

For each kind of hypertension, there is a single underlying cause. The causes of hypertension provide information on a condition or the effects of medication (Ding and Zhang, 2019). Secondary hypertension occurs when there is a clear cause right away. It is possible to have both essential and secondary hypertension, particularly when there is a rapid deterioration of blood pressure regulation. Adrenal disease, kidney disease, obstructive sleep apnoea, pheochromocytoma or paraganglioma, pregnancy toxemia, and thyroid disease are all potential causes of secondary hypertension, all of which shall be discussed later in this paper (Ding and Zhang, 2019).

Secondary hypertension may be caused by a number of other diseases such as diabetes complications (diabetic nephropathy). It is possible that diabetes will cause hypertension by damaging the kidneys' filtering structure. Cats and dogs with polycystic kidney disease are also at risk of developing secondary high blood pressure (Lin *et al.*, 2019). Growths in the kidneys prevent normal renal function in this acquired ailment, which increases blood pressure. Another cause of HBP in animals is glomerular infection. The glomeruli, which are

microscopic tubes that carry waste and salt out of the kidneys, may grow in certain people and animals. Hypertension may develop if the larger glomeruli are unable to function normally (Fan *et al.*, 2021). Renovascular hypertension, a kidney disease, is also a common cause of high blood pressure in animals. This kind of hypertension is caused by a narrowing (stenosis) of one or both kidney-sending pathways (AlMarabeh *et al.*, 2019). As with coronary artery disease, renal hypertension may be caused by fatty plaques (atherosclerosis) or by thickening and solidification of the renal arteries' smooth muscle and sinewy tissues (fibromuscular dysplasia) (Fang, 2021).

Ailments that affect the hormonal balance may also lead to further hypertension. Cushing's condition is one such possibility. A pituitary tumour or other factors that can cause the adrenal glands to generate a lot of the chemical cortisol might create secondary hypertension in this situation (Hall *et al.*, 2019). Additionally, hypertension is caused by aldosteronism, which is a hormonal disorder that affects both humans and small animals (Hall *et al.*, 2019). Aldosterone is a substance produced in large quantities by the adrenal glands. Salt and water build up in the circulatory system of the body, resulting in an increase in circulatory blood pressure. Pheochromocytoma, a common occurrence in animals, is also a common occurrence in humans. Normally located in the adrenal gland, this intriguing growth produces a large amount of the chemical adrenaline and noradrenaline, which may lead to long-term hypertension or brief increases in blood pressure (Fan *et al.*, 2021). In addition, this issue will be extensively discussed in the article.

Thyroid disorders (especially hyperthyroidism) are the most common causes of hypertension in dogs and cats. Hypertension may occur if the thyroid gland is unable to produce enough thyroid hormones (hypothyroidism) or if it provides an excessive quantity of thyroid hormones (Holland *et al.*, 2020). Coarctation of the aorta is another possible cause of secondary hypertension. Secondary hypertension occurs when there is a pre-existing disease or disorder. It is possible to have both essential and secondary hypertension, particularly when there is a rapid deterioration of blood pressure regulation (Ding, and Zhang, 2019). Adrenal disease, kidney disease, obstructive sleep apnoea, pheochromocytoma or paraganglioma, pregnancy toxemia, and thyroid disease are all potential causes of secondary hypertension (Ding, and Zhang, 2019). It can occur in newborn pups or kittens and babies with aorta coarctation in which the pressure at which the heart has to forcefully pump blood through the constrained vessel into the systemic circulation is heightened (Coleman and Brown, 2020). Consequently, the heart rate increases, particularly in the arms. Rest apnoea is another common clinical condition in animals. The condition is typically marked by severe wheezing and breathing, preventing it from receiving enough oxygen.

The vascular endothelium can be damaged by a lack of oxygen, making it more difficult for the arteries to control the blood pressure. Another effect of sleep apnoea is an overactive sensory system that releases hormones that raise the heart rate (Dempsey *et al.*, 2010).

Weight gain and pregnancy are the most common causes of hypertension in humans and pets, including cats, dogs, and rats. The blood vessels become stenotic, increasing the blood pressure. The arteries have a tougher time moving blood when the animal is overweight, which exacerbates the high blood pressure. Also, synthetic drugs that elevate blood pressure may be delivered through fat storage (Holt, 2020). Pregnancy is a state in which hypertension may be exacerbated or initiated. Hypertension is a common occurrence in gravid animals (pregnancy-initiated hypertension or toxemia) (Andrea *et al.*, 1997).

ENDOCRINE DISEASES

Hormones serve critical roles in blood pressure regulation, cardiovascular regulation and homeostasis in cats and dogs. Alteration in the production and regulation of these hormones can cause adverse effects on the functions and the system they regulate therefore causing alterations and diseases such as hypertension. Some of the endocrine diseases like pheochromocytoma, hyperaldosteronism, hyperthyroidism, and acromegaly have effects on blood pressure.

Pheochromocytoma

Pheochromocytoma is a kind of tumour that grows in the adrenal glands or in certain nerve cells of the nervous system. The abnormal growths of the secretory cells produce catecholamines in excessive amounts and that will result in emotional symptoms (Holt, 2020). Pheochromocytoma may arise in nerve cells, although most of the time they are found in one or both of the adrenal glands. The ability of these growths to distribute chemicals necessitates treatment even when they are not malignant. Catecholamines, which are vasoactive substances that cause vasoconstriction which increases blood pressure are produced by pheochromocytoma, which are cancerous tumours in the adrenal gland (Hughes *et al.*, 2020). There are three hormone mixes that are particularly well-known for increasing circulatory strain: adrenaline or epinephrine, noradrenaline or norepinephrine and dopamine. Small doses of these synthetic compounds are often used by the body to respond to dangerous or uncomfortable situations.

Even in little doses, all three substances have a noticeable influence on heart rate. Emotional effects on blood pressure are typical in patients with pheochromocytoma

because they create a large amount of these substances. Most humans, dogs and cats with pheochromocytoma have elevated blood pressure, and this illness causes extravagant fluctuations in blood pressure over the day, which is an indication of hypertension. Pheochromocytoma is characterised by three main symptoms, including headache, excessive sweating, and fast heart rate (Bishop *et al.*, 2021). The most common adverse effect of pheochromocytoma is an increase in blood pressure. Other less frequent symptoms include blurred vision, weight loss, polydipsia, polyuria and elevated glucose levels. These symptoms may be caused by a variety of illnesses, so proper clinical examination and laboratory test will be required by veterinarians for effective management of this condition in dogs and cats.

Hyperaldosteronism

Hyperaldosteronism is a disease in which the adrenal glands overproduce aldosterone, resulting in high blood pressure and low potassium levels in the blood. Essential hyperaldosteronism is possible when one or both adrenal glands are overactive (unilateral or bilateral). Adenoma is the most common cause of one-sided sickness, but adrenal disease or hyperplasia is less common (when the entire organ is hyperactive). Reciprocal hyperplasia is often responsible for causing respective illnesses (when the two organs are hyperactive) (Ogoh and Tarumi, 2019). Some rare inherited diseases such as familial hyperaldosteronism types I and II may cause the two organs to overwork (Ogoh and Tarumi, 2019).

When hyperaldosteronism is present, high blood pressure is the most common symptom. Dogs and people with severe hypertension may need four or more medications to manage their condition. Anxiety and drowsiness are all possible symptoms of high blood pressure. Most patients with hyperaldosteronism may have potassium levels that are within the normal range, although this is not always the case. Exhaustion, deadness, expanded urine, expanded thirst, muscular problems and muscle shortfall are all symptoms of hypokalaemia (Holland *et al.*, 2020). This condition raises the risk of heart attacks, strokes, cardiovascular breakdowns, renal failure, and early death in dogs and cats.

Hyperthyroidism

Overproduction of thyroid hormones causes hyperthyroidism (an overactive thyroid gland). High level of thyroid hormone in circulation results in an increased metabolic rate. Hyperthyroid felines and canines are at increased risk for a variety of cardiovascular problems, including atrial fibrillation, hypertension, coronary artery disease, stroke, cardiovascular collapse, anxiety,

palpitation, hyperthermia, sleeping difficulty, and weight loss despite being famished all the time are common symptoms (Fang, 2021). Hyperthyroidism, when left untreated, does more injury to the heart of dogs than only having it beat faster. Hyperthyroidism is caused by the excessive production of thyroid hormones by the thyroid glands (Kiuchi *et al.*, 2019). Systolic blood pressure increases as a result of the heart's constrictive strength (Lombardi *et al.*, 2018).

Oxygen-starved cardiac muscles demand more oxygen as the heart pumps more blood and beats harder. Hyperthyroidism can also cause *angina pectoris* or ischaemic chest pain in men and animals, which is caused by the inability of the coronary arteries to deliver adequate blood to the heart muscle in order to meet its needs (Claassen, 2021).

In addition, an overactive thyroid may exhaust the heart by making it work harder and faster, leading to cardiovascular breakdown, hypertrophic cardiomyopathy, and heart failure, especially in cats.

Acromegaly

Chronic hypersecretion of growth hormone (GH) causes a disorder known as acromegaly. This condition's clinical features, such as significant growth and metabolic dysfunctions as well as long-term tissue openness to GH overabundance-related complications such as cardiovascular infection, diabetes and respiratory issues and arthritis are all well documented (Ding and Zhang, 2019). Standard antihypertensive medications work well in controlling hypertension in acromegaly.

Acromegaly is characterised by bleakness and mortality that is exacerbated by the presence of hypertension. The prevalence of hypertension in acromegalic patients ranges from 18 to 60 per cent, and it is more common than in the general population. An association between increased Insulin-like Growth Factor 1 (IGF-I) and Growth Hormone (GH) levels and hypertension has been suggested by the reduction in GH levels after successful therapy for acromegaly (Iturriaga and Castillo-Galán, 2019). Hypertension in acromegaly is still a mystery, although a number of factors may play a role, including the animal's chronic exposure to GH and IGF-I excess. Excessive growth hormone in circulation results in insulin resistance, hyperinsulinaemia, increased vascular resistance and plasma expansion in dogs and cats, thus resulting in hypertension (Iturriaga and Castillo-Galán, 2019).

HEART DISEASES

Hypertension can be caused by anatomic and structural abnormalities in the blood vessels and it can result in other cardiomyopathies especially hypertrophic cardiomyopathy and myocardial infarction.

Vascular defect

Prevalence of peripheral vascular disease (PVD) has been linked to a high rate of cardiovascular risk and death. One of the most common and major risk factors for vascular disorders like PVD is high blood pressure (Lombardi *et al.*, 2018). Around 2 to 5% of hypertensives have discontinuous claudication, and this prevalence increases with age. As a result, 35 to 55% of patients with PVD also have hypertension at the time of diagnosis. There is an immensely increased risk of myocardial infarction and stroke for patients with PVD who suffer from hypertension. Hypertension contributes to the pathogenesis of atherosclerosis, the essential hidden obsessive cycle of PVD, in addition to its epidemiological linkages (Hall *et al.*, 2019). Hypertensive patients and dogs are more likely to develop atherosclerosis because of abnormalities in haemostasis and lipids (Hall *et al.*, 2019).

High systolic blood pressure, in particular, is a strong risk factor for heart disease and stroke. Even as long back as 1962, an actuarial investigation uncovered that these complexities are more strongly linked to the systolic rather than diastolic blood pressure increase. No correlation between diastolic blood pressure and cardiovascular death was found in the Glasgow Blood Pressure Clinic. (Lip *et al.*, 2019) A reduction in systolic blood pressure reduces mortality from all causes, although it remains 2 to 5 times greater than the mortality rate in the general population (Ogoh and Tarumi, 2019).

RENAL DISEASES

Renovascular hypertension

Hypertension resulting from kidney disease is known as renal renovascular hypertension or renovascular hypertension. Anti-hypertension medications can, for the most part, control it (Saxton, 2019). Patients with renal hypertension may benefit from angioplasty, stenting, or other medical procedures on the renal veins, depending on their specific situation. Persistent infections of the kidneys might be caused by renal hypertension (Saxton, 2019). At that stage, the glomerular filtration rate is slow. The ongoing renal disease also has no negative effects until the situation is at the cutting edge.

A narrowing of the arteries that carry blood to the kidney causes renal hypertension. Stenosis of one or both kidneys' blood vessel(s) may be caused by various medical conditions. A reduction in the quantity of blood flowing through the kidneys makes them act as if the problem is due to dehydration. In this regard, they respond by sending substances that stimulate the body to retain salt and water. As the veins fill with additional fluids, the heart's rate increases. Atherosclerosis, or hardening of the arteries, is the most common cause of kidney obstruction.

Many respiratory failures and strokes are caused by this cycle. Fibromuscular dysplasia is a less prevalent cause of stenosis (AlMarabeh *et al.*, 2019). As a result of this disorder, the renal supply channels develop abnormally for unknown causes.

Autosomal dominant polycystic kidney disease

By altering the vascular endothelium and activating chemicals that govern the blood pressure, Autosomal Dominant Polycystic Kidney Disease (ADPKD) may increase blood pressure. Not only are the kidneys affected by the Polycystic Kidney Disease (PKD1 and PKD2) defects that cause ADPKD, but the blood vessels' outer sheaths are also affected. When these features are not working correctly, the vessels' ability to repair and unwind might be slowed. Blood vessels are generally smaller and tighter than predicted in dogs with ADPKD. Smaller blood arteries restrict the flow of blood, increasing the amount of load on the circulatory system (Fan *et al.*, 2021). It may be likened to a freeway where a route has been closed, causing traffic to become more congested.

ADPKD may also activate molecules that regulate blood pressure (for example angiotensin II). These compounds may be used for a variety of reasons. If, for example, renal growths obstruct blood vessels in the kidney, blood flow will be impeded (Holt, 2020). When blood flow is cut off, this might lead to an increase in the amounts of certain substances in the body. As kidney cysts form and the kidneys enlarge, hypertension is likely to worsen.

Renal failure

Uncontrolled hypertension may weaken, debilitate, or harden the renal arteries over time. There is not enough blood getting to the renal tissue because of the damaged blood vessels. Damaged kidney vessels are unable to effectively transport blood. Blood is channeled through the kidneys by tiny, finger-like structures called arterioles and glomerular capillaries. It is the tiniest of all arteries that each nephron receives its blood supply. When the blood vessels are damaged, the nephrons are deprived of oxygen and nutrients (Bishop *et al.*, 2021). They lose their ability to control blood flow and fluid, chemical, acid and salt concentrations in their bodies at this moment (Bishop *et al.*, 2021).

Injured kidneys are unable to regulate blood pressure. Aldosterone, a hormone produced by the adrenal glands, helps the body regulate blood pressure by guiding the flow of blood through the kidneys (Holland *et al.*, 2020). A negative twist is exacerbated by kidney damage and unchecked hypertension (Holland *et al.*, 2020). The kidneys eventually fail when more pathways get blocked and stop operating.

OBESITY

Obesity may cause hypertension and increased cardiovascular risk. The neuroendocrine system, as well as fat-derived components, are still considered to have an important role. Being overweight may lead to cardiovascular disease in dogs and cats by activating the renin-angiotensin-aldosterone framework, increasing cognitive activity, increasing insulin resistance, increasing procoagulant movement and breaking down the vascular endothelium (Saxton, 2019). If people have obesity-related hypertension, they are more likely to have insulin resistance and glucose intolerance as well. Specifically, 2% of treated hypertensive patients are diagnosed with diabetes each year (Sultan, 2018). In addition, the risk of cardiovascular disease increases with the onset of type 2 diabetes. Recently discovered diabetes has the same antagonistic impact as well-documented diabetes. These metabolic anomalies may not only play a role in cardiovascular disease, but they may also contribute to numerous renal injuries (Sultan, 2018). Vascular and insulin resistance have recently been suggested by Saxton (2019), as contributing factors in the early stages of renal failure in hypertensive patients, a condition formerly known as hypertensive nephrosclerosis (Sultan, 2018).

Obesity is linked to an increased risk of cardiovascular disease; however, this assumes that obesity and hypertension are present. Except in cases of hypertension, the cardiovascular risk does not significantly increase in obese or overweight individuals. Hypertension is more common in big animals, but people with hypertension also seem to be more prone to weight growth. Weight growth in hypertensive patients is more likely than in non-hypertensive patients (Framingham and Tecumseh, 1993). This means even normal weight hypertensives have a significant risk of becoming obese (Atefi *et al.*, 2021).

PREGNANCY

Pregnancy hypertension is currently described by a plethora of terminologies, some of which are quite detailed and point by point. Even the single ingredient here designated as "toxaemia" has been described by many producers under the headings of blood poisoning; xerostomia; pregnancy-prompted hypertension; and pregnancy-related hypertension (Lombardi *et al.*, 2018). The American College of Obstetricians and Gynaecologists' 1972 approach was recommended by the Working Group. Pregnancy-related hypertension may be divided into four categories: toxaemia and eclampsia, continual hypertension (for whatever cause), toxaemia with persistent hypertension, and transitory hypertension (Lombardi *et al.*, 2018). This may be used as related to both humans and small animals, such as dogs and cats.

When paired with continuous hypertension or renal illness, toxemia is the most significant threat to foetal health and is typically associated with maternal complications. Fundamental hypertension is the most common underlying condition in pregnant animals that suffer from chronic hypertension. In most cases, the hypertension is mild and the pregnancy is straightforward in these criteria (Fang, 2021). Chronic hypertension may be caused by a variety of different endocrine disorders or even by something as simple as a basic kidney infection. Pregnancy may be a challenge for some dogs 'with these optional forms of hypertension'. As an example, the symptoms of Cushing's disease might be increased, and the embryo's development would be obscured (Fang, 2021). However, when detected in an easy-to-understand manner, the infection may be managed pharmaceutically until delivery, after which operable malignancies are removed. The presence of pheochromocytoma is associated with a high rate of maternal and foetal death (Sultan, 2018).

MECHANISM OF HYPERTENSION DEVELOPMENT

Vascular regulation

For established hypertension, increased Peripheral Vascular Resistance (PVR) is an indicator, although heart rate changes may likely play a role. The heart's pulsatile stream may be dampened by large, flexible passageways. In the arteries, pressure wave reflection from the downstream side might elevate brachial systolic blood pressure contrasted and focalized aortic systolic blood pressure and this changes the tension waveform (Ding and Zhang, 2019). An extension (attractions) wave is responsible for the closure of the aortic valve when the left ventricular constriction slows down. High blood pressure causes the heart and arteries to regenerate and become larger (Ding and Zhang, 2019). A loss in myocardial fibre capacity may be compensated for by this method, which normalises left ventricular and blood vessel wall stress. The veins of hypertensive patients are not stiffer than those with normal blood pressure. As blood arteries enlarge, they become stiffer, and this is mirrored by the increased solidity in hypertension (Tian, and Liang, 2021). Hypertension is associated with a reduction in microvascular thickness and a decrease in vascular vasodilators (Tian and Liang, 2021).

Nitric oxide

Sicknesses like coronary heart disease and cancer are linked to stress, which is seen as a risk factor for many other societal infections. There is a lot of interest in research that examines the instruments connected with

pressure-induced hypertension, but the results have not yet been conclusive about the causal link between stress and long-term elevation in blood pressure (Fang, 2021). Stress-induced hypertension has been linked to a number of factors, including the increased movement of the sympathetic nervous system (SNS), glucocorticoid overburden, altered endothelial capacity, and decreased nitric oxide (NO) bioavailability, according to a few studies (Ding and Zhang, 2019). The vasodilator, neuromodulator, and synapse nitric oxide play an important role in the regulation of neuroendocrine instruments and the heart's response to stress (Ding and Zhang, 2019). Thus, NO plays an important role in blood pressure regulation and control. One way to look at elevated NO level is as a pressure-restricting tool that works to help the body recover from stress and return to resting levels by reducing the sympathetic nervous system activities and expanding NO-dependent vasorelaxation (Ding and Zhang, 2019). As a result, NO bioavailability would reduce later under stress and in participants with a familial predisposition to hypertension, both of which would indicate a disruption of the NO-dependent blood pressure control system and an increased sympathetic nervous system and glucocorticoid influence (Ding and Zhang, 2019).

Bradykinin

Cardiovascular diseases such as coronary artery disease, congestive heart failure, and peripheral vascular and kidney infections may all be accelerated by high blood pressure. Bradykinin's role in the development of hypertension is well documented. Its pharmacological effect includes vasodilatation in several regions of the circulation, a reduction in all-out fringe vascular resistance and guidance of salt discharge from the kidney (Hall *et al.*, 2019). Diarrhoea and natriuresis are induced when bradykinin is injected into the renal arteries (Hall *et al.*, 2019). Bradykinin's actions have been attributed to renal prostaglandin discharge (Hall *et al.*, 2019). To date, bradykinin has been assigned the task of reducing urine kallikrein discharge in hypertensive people and animals. This led to the hypothesis that a decrease in urine kallikrein discharge in hypertension conditions may be caused by a flaw in kinin ageing (AlMarabeh *et al.*, 2019).

Research on bradykinin's underlying alterations has provided new insights into the components of various hypertension situations. Kininogen levels and a kinin-potentiating factor are known to be decreased in basic and dangerous hypertension (AlMarabeh *et al.*, 2019). Hypertension's aetiology may be complicated by a deficiency in the bradykinin framework. This group suggests that the renal kallikreins' role is to excrete excess salt (AlMarabeh *et al.*, 2019). As a result, a reduction in renal kallikreins activity may relieve hypertension by reducing salt accumulation in the body. As a result,

developing a chemical with renal kallikrein-like activity might help the kidneys successfully eliminate excessive salt. Man and animals suffering from hypertension may benefit from this exercise (AlMarabeh *et al.*, 2019).

Endothelin

Endothelin is a potent vasoconstrictor peptide that serves a variety of other functions throughout the body. The most abundant and important among these categories of peptides in blood vessels, is endothelin-1 (ET-1). Salts induced hypertension models increase ET-1 production in the endothelium and kidney (Barnet, 2016) (e.g.: DOCA-salt rodents and Dahl salt-touchy rodents, in salt-stacked spontaneous rats in angiotensin II-mixed and in diabetic rodents). It is via the expansion of oxidant stress in the vasculature's partition that ET-1 provokes an inflammatory response, resulting in vascular remodeling and endothelial breakage in hypertension models with endothelin-intervened parts. In hypertensive conditions, endothelin receptor blocker reduces blood pressure and vascular hypertrophic remodeling. The vascular articulation of ET-1 is improved in patients with stage 2 hypertension (Hughes *et al.*, 2020). The blood pressure of hypertensive dog and cat can be lowered by antagonists of the endothelin receptor. When it comes to treating hypertension and type 2 diabetes, endothelin receptor blockers can be used for the prevention of organ damage to the target organs (Hughes *et al.*, 2020). Endothelin receptor blockers have slowed the development of these symptoms to this point. Alternatively, endothelin-blocking drugs that prevent the endothelin-changing over processes that generate ET-1 may become available in the future. The endothelin framework plays a crucial role in the rapidly fatal disease of essential pulmonary hypertension (Barnet, 2016).

Angiotensin II

The major actions of Angiotensin II (Ang II) include vasoconstriction, cognitive anxiety, increased aldosterone biosynthesis, and renal activity, all of which elevate blood pressure. Ang II is also involved in the acceptance of vascular smooth muscle cell growth, cell motility, and mitosis, as well as the enlarged union of collagen types I and III in fibroblasts, leading to the thickening of the vascular walls and myocardium and fibrosis (Ogoh and Tarumi, 2019). Type 1 Ang II receptors (AT1) are involved in these processes, and losartan, an AT1 receptor blocker, will inhibit the process. Researchers have shown that Ang II plays an important role in hypertension and the pathophysiology of vascular damage during high blood pressure (Ogoh and Tarumi, 2019). Ang II is also linked to the progression of atherosclerosis and to the renovation

and repair cycles of the myocardium when cardiac localised necrosis has occurred (Ogoh and Tarumi, 2019). As a last note, the neurohumoral induction of cardiovascular disease is aided by increased Ang II concentrations. Angiotensin-converting enzyme (ACE) and angiotensinogen polymorphisms have been linked to an increased risk of cardiac death, hypertension, and left ventricular hypertrophy, according to recent findings (Sultan, 2018).

Vasopressin

The nerve centre is where Vasopressin, also known Anti-diuretic hormone (ADH), is controlled. Because it includes arginine, the human molecule is known as arginine vasopressin (AVP). Vasopressin receptors are classified as V1A, V1B, or V2, and all three are G-protein coupled. Through its critical physiological influence on water maintenance and a reduction in the viable osmotic tension of bodily liquids, ADH increases the penetrability of renal collection channels (Sultan, 2018). Increased strong osmotic plasma pressure, decreased extracellular fluid volume, discomfort, feeling ill, and spitting all stimulate vasopressin release; while, decreased successful osmotic plasma pressure, increased extracellular fluid volume, and alcohol consumption all limit it (Sultan, 2018). Vasopressin receptor blockers decrease vascular smooth muscle constriction and have diuretic effects (V2 receptor blockers) (Sultan, 2018). The two drugs are now being tested in clinical trials.

Renal regulation

Aldosterone

Aldosterone is a steroid hormone produced mostly in the adrenal cortex, although it is also found in other parts of the body. Aldosterone's mineralocorticoid effect is many times more significant than that of cortisol, although cortisol's plasma convergence is many times greater than that of aldosterone (Fang, 2021). K⁺ release by renal rounded epithelial cells may be enhanced by aldosterone in the collecting tubules, as well as in the distal convoluted tubules and collecting ducts, although not to the same extent (Fang, 2021). Afterwards, aldosterone protects the extracellular Na⁺ and increases the urine K⁺ outflow.

Chronic glomerulonephritis

Hypertension is a common complication of renal disease. A decrease in glomerular filtration rate (GFR) leads to hypertension in almost all people as well as dogs and cats that have it. Chronic Glomerulonephritis (GN), GN

recurrence, diabetes nephropathy, polycystic kidney infection and hypertensive nephrosclerosis all contribute to renal parenchymal hypertension (Ding and Zhang, 2019). A larger percentage of people, dogs and cats with severe GN, such as post-streptococcal GN1, develop mild to moderate hypertension. Hypertension occurs only in animals with high levels of GN because sodium retention causes liquid overload, as seen by the concealment of the renin-angiotensin-aldosterone (RAAS) signaling cascade (Tian and Liang, 2021).

There is an increased risk of developing hypertension in men and small animals with ongoing glomerulonephritis (GN). Chronic GN hypertension is mostly caused by an increase in blood volume rather than a decrease in renal function. As renal damage, particularly arteriolosclerosis, progresses and renal ischemia results, patients with continuous GN experience the sensation of the intrarenal renin-angiotensin-aldosterone framework (RAAS) (Hall *et al.*, 2019). Hypertension in continuous GN is exacerbated by the overactivity of the cognitive sensory system. It was recommended that pets and people with chronic kidney disease but no albuminuria should have objective blood pressure (BP) of 140 mmHg systolic and 90 mmHg diastolic (Tian and Liang, 2021). With excretion of albumin at the rate of 30 mg/24h, suggested a lower pressure of 130 mmHg systolic blood pressure and 80 mmHg diastolic blood pressure in many patients (i.e., those with both micro and macro albuminuria) (Sultan, 2018). People and pets with an albumin discharge rate of 30 mg/24h should be treated with RAAS-blocker (Hall *et al.*, 2019). Using a calcium channel blocker and diuretic in conjunction with a RAAS blocker might help individuals with chronic GN achieve their target blood pressure and reduce the amount of urine protein they produce.

Mineralocorticoid

Extensive hypertension and hypokalaemia are often seen in dogs and cats with mineralocorticoid excess. Essential aldosteronism is the most prevalent cause of mineralocorticoid excess, accounting for around 10% of cases of essential hypertension and up to 20% of cases of secondary hypertension (Atefi *et al.*, 2021). Essential aldosteronism causes an oversupply of cardiovascular bleakness in comparison to the same essential hypertension. Increased numbers of Na⁺-permeable epithelial Na⁺ channels in the distal renal tubule and cortical collecting tubules are the result of mineralocorticoids acting on cells in these regions (Epithelium sodium channel) (Saxton, 2019). To this end, they also stimulate the basolateral Na⁺/K⁺-ATPase syphon in order to cause a dynamic Na⁺ reabsorption process and the loss of K⁺ into the urine. Extracellular liquid volume and blood pressure are both increased when water is latently reabsorbed with Na⁺ (Saxton, 2019).

Endocrine/hormonal regulation

Aldosterone

In addition to its role in salt and water balance and the regulation of circulatory strain, aldosterone plays an important role in cardiovascular remodeling via the mineralocorticoid pathway. Aldosterone-induced renal sodium reabsorption may be affected by both genetic and non-genomic instruments (Sultan, 2018). Furthermore, the mineralocorticoid receptor has recently been discovered in non-epithelial tissues, such as the heart and vascular smooth muscle cells. Thus, aldosterone is likely to have a variety of pleiotropic effects that contribute to the adjustment of blood pressure (Sultan, 2018). There is a shockingly high prevalence of essential hyperaldosteronism among pets with hypertension as a general rule and among those with more severe or mild hypertension in particular. Aldosterone antagonists have been found to be effective in lowering blood pressure in men, dogs and cats. (Sultan, 2018). Aldosterone fixation and the aldosterone to renin ratio have been demonstrated to predict a greater risk of developing hypertension in non-hypertensive persons in recent area-based examinations (Sultan, 2018). Mineralocorticoids have an important role in hypertension development, as shown by the combination of the aforementioned perspectives.

CONCLUSION

In conclusion, knowledge of blood pressure regulation mechanisms is important in the in-depth understanding of the pathophysiology of hypertension and molecular mechanisms of hypertension and other cardiovascular diseases. This will enhance diagnosis, research activities and clinical management of hypertension and cardiovascular diseases. It will also help clinicians to understand other conditions that are predisposed to or co-exist with cardiovascular diseases, thus enhancing their precise diagnoses and treatments. The review also highlights the endocrine and vasoactive agents critical to organ dysfunction and pathology seen in cardiovascular diseases. Serum levels of those specific hormones, proteins and vasoactive agents are measurable by using specific assays. These then serve as specific biomarkers useful in diagnostic and research findings by clinicians and cardiologists.

It is, therefore, recommended that clinicians and cardiovascular system researchers have an in-depth understanding of these molecular mechanisms for better research outputs and comprehensive clinical management.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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