Hypertension Demystified: A Comprehensive Review

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Running Title: Systematic Review on Hypertension with its Complications, Pathophysiology, Pre-clinical Models (*In-vivo* & *In-vitro*) and BP Monitoring parameters.

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Abstract

Hypertension (HTN) is a leading risk factor for cardiovascular diseases and mortality, affecting 1 billion people worldwide and causing up to 9 million deaths annually. Often called the "silent killer," it results from a complex mix of genetic and environmental factors.

This review provides an overview of key rodent models used in hypertension research, including recent advances in blood pressure monitoring techniques. It covers the complications and pathophysiology of hypertension, the roles of various factors, and the use of preclinical models (both *in-vivo* and *in-vitro*). We discuss genetic, transgenic, and ecological rodent models, emphasizing the importance of reliable blood pressure measurement methods. Common techniques include non-invasive methods like the Tail Cuff and Electrocardiography, and invasive methods such as Carotid Artery Cannualation and Caudal Ventral Artery monitoring. While intra-arterial catheters offer greater accuracy, they require surgical procedures. The review also addresses emerging technologies in blood pressure monitoring.

In summary, traditional and genetic animal models provide crucial insights into hypertension, helping researchers understand its mechanisms and develop potential treatments.

Keywords: *Hypertension, Pre-clinical model, Pathophysiology, Transgenic, In-vivo, In-vitro*

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Introduction:

Hypertension is the most prevalent modifiable risk factor for cardiovascular diseases (CVD) and mortality. The risks associated with elevated blood pressure (BP) can be significantly reduced through antihypertensive medications, which lower BP and mitigate target organ damage.[1] Prolonged high arterial pressure leads to severe pathological changes in the vasculature and cardiovascular system. A blood pressure reading of ≥140/90 mmHg indicates a high risk for hypertension-related cardiovascular disease, necessitating prompt medical intervention.[2]

The Eighth Joint National Committee (JNC 8) guidelines recommended initiating antihypertensive therapy (AHT) to reduce diastolic blood pressure (DBP) below 90 mmHg in individuals aged 30 to 59 years, and to maintain BP below 150/90 mmHg in hypertensive patients aged 60 years or older.[3] Hypertension, often called the "silent killer," affects over 1 billion people worldwide and is responsible for up to 9 million deaths annually.[4] Besides its significant health burden, hypertension management and prevention also have substantial socioeconomic implications.

Previous reviews have focused on the utility of experimental models in understanding the phenotypic and genomic aspects of hypertension. The development of common models and recent advancements in molecular genetics and genomics has introduced powerful tools for investigating the genetic underpinnings of complex diseases like hypertension. Specifically, various rat models have been instrumental in identifying susceptibility markers.[5] Blood pressure is a critical parameter for evaluating cardiovascular function in rodents, typically measured using invasive, non-invasive, and radio telemetry methods, with invasive blood pressure (IBP) recording being the preferred standard for directly assessing the impact of investigational products on the circulatory system.[6]

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This review explores the complexities of hypertension, including its complications, pathophysiology, and the preclinical models used to evaluate it. We also discuss various methods for measuring and controlling blood pressure, as well as monitoring hypertension. Finally, examined the current advancements in hypertension models and identify areas that still require further investigation.

Complications of Elevated Blood Pressure

Hypertension significantly increases the risk of various health complications, primarily due to the chronic pressure it puts on blood vessels and organs. Here's how elevated blood pressure contributes to these complications:

Heart Problems:

Angina and Heart Disease:

Hypertension can lead to changes in the structure and function of the heart, commonly referred to as hypertensive heart disease. The sustained high blood pressure exerts excessive force on the arterial walls, leading to damage and potential blockage of arterioles. This increases the risk of heart attacks. Prolonged hypertension causes left ventricular hypertrophy, a thickening of the heart muscle that eventually leads to heart failure, both systolic and diastolic. Eccentric hypertrophy raises the myocardium's oxygen demand, which can manifest as angina or ischemia. Additionally, muscle hypertrophy can disrupt the heart's electrical conduction system, increasing the risk of atrial fibrillation and ischemic stroke.[7, 8, 9]

Stroke:

Increased Stroke Risk: Hypertension is a major risk factor for stroke. High blood pressure can cause arteries to narrow or become blocked, impeding blood flow and oxygen delivery to

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the brain. In severe cases, blood vessels may rupture, leading to haemorrhagic stroke. Hypertension is also linked to an increased risk of dementia, particularly after a stroke, due to the damage to brain tissue. Stroke remains a leading cause of death and severe long-term disability, with many first-time stroke patients having a history of hypertension.[9, 10]

Kidney Damage:

Hypertension-Induced Kidney Disease: High blood pressure can compress the arteries in the kidneys, eventually leading to kidney damage and disease. Over time, hypertension diminishes the kidneys ability to filter blood efficiently, causing the build up of waste products that are normally excreted through urine. The combination of kidney disease and hypertension can create a vicious cycle, where kidney damage further elevates blood pressure, potentially leading to kidney failure.[11]

Metabolic Syndrome:

Hypertension and Metabolic Disorders: Metabolic syndrome is characterized by a cluster of conditions, including abdominal obesity, high blood pressure, hyperglycaemia, high blood lipid levels, and an increased risk of heart disease. Individuals, who are overweighting, obese, have dyslipidaemia, or type 2 diabetes have at a significantly higher risk of developing hypertension. The interplay between these metabolic disorders and high blood pressure increases the overall cardiovascular risk.[12, 13]

Peripheral Artery Disease (PAD):

Hypertension and Atherosclerosis: Chronic hypertension can contribute to the development of atherosclerosis, where cholesterol builds up in the arteries, leading to peripheral artery disease (PAD). PAD is particularly dangerous as it involves the narrowing of arteries in the lower limbs, reducing blood flow and increasing the risk of pain, ulcers, and, in severe cases, gangrene. PAD is often associated with atherosclerotic disease of the abdominal aorta, iliac,

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and femoral arteries, where atherosclerotic plaque slowly accumulates, eventually restricting arterial blood flow.[7, 14]

Eye Disease:

a) Ocular Complications: Untreated or poorly managed hypertension can lead to several eye conditions, which may result in vision loss.

b) Choroidopathy: This condition, caused by fluid accumulation under the retina, can lead to distorted or reduced vision.

c) Optic Neuropathy: Reduced blood flow to the optic nerve can cause optic neuropathy, leading to irreversible vision loss.

d) Retinopathy: Hypertensive retinopathy occurs when reduced blood flow damages the retina, potentially causing vision impairment or blindness in severe cases.[15]

Sexual Dysfunction:

Impact on Sexual Health: Normal blood pressure is essential for sexual function. Hypertension can reduce blood flow to the pelvic region, leading to decreased libido. In men, this often manifests as erectile dysfunction (ED), while women may experience fatigue and vaginal dryness. Hypertension is one of the most significant risk factors for ED, which in turn is linked to an increased risk of cardiovascular disease.[16]

Pathophysiology of Hypertension

Arterial pressure influences heart rate and systemic vascular resistance. Peripheral resistance can be modified by regional factors such as pH, hypoxia, and physiological agents (angiotensin II, catecholamines, coagulants, etc.), while cardiac output is determined by

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blood flow, atrial function, central nervous system neurotransmitters, and cardiac properties (rhythm and contraction). In response to decreased arterial pressure, renin is secreted by the juxtaglomerular cells of the kidneys, leading to the conversion of angiotensinogen in the liver to angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme primarily in the lungs. Angiotensin II acts as a potent vasoconstrictor and stimulates aldosterone secretion from the adrenal cortex, resulting in increased sodium reabsorption. Additionally, peptides from the adrenal glands promote water reabsorption, which increases arterial volume and pressure.[17]

Portal hypertension is associated with alterations in intrahepatic, systemic, and porto-systemic collateral circulation. The pathogenesis involves changes in vasoreactivity, specifically enhanced vasodilation and vasoconstriction, leading to increased intrahepatic resistance, hyperdynamic circulation, and collateral vessel formation. Nitric oxide (NO), a critical vasoactive substance, functions as a major vasodilator. Conversely, vasoconstrictors such as prostaglandins produced by cyclooxygenase and endothelin-1 contribute to elevated vascular tone. The imbalance between excessive production of vasoconstrictors and inadequate production of vasodilators underlies the increased vascular resistance in the hepatic sinusoidal region.[18]

Renal hypertension is primarily driven by the activation of the renin-angiotensin-aldosterone system. In chronic kidney disease (CKD), renin levels may appear "inappropriately normal," indicating they are not elevated relative to the degree of hypertension and fluid overload. Elevated serum renin activity is typically observed in cases with nephron capillary constriction. Increased renin levels may result from its sequestration in poorly perfused areas such as lesions or scars, or may be influenced by micro angiopathic damage or tubule interstitial inflammation. This condition raises blood volume and systemic

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vascular resistance through angiotensin II mediated vasoconstriction and aldosterone-induced sodium retention. Elevated angiotensin II levels also contribute to meningeal cell proliferation, fibrosis, endothelial damage, inflammation, and cardiac hypertrophy, exacerbating hypertension and end-organ damage.[19]

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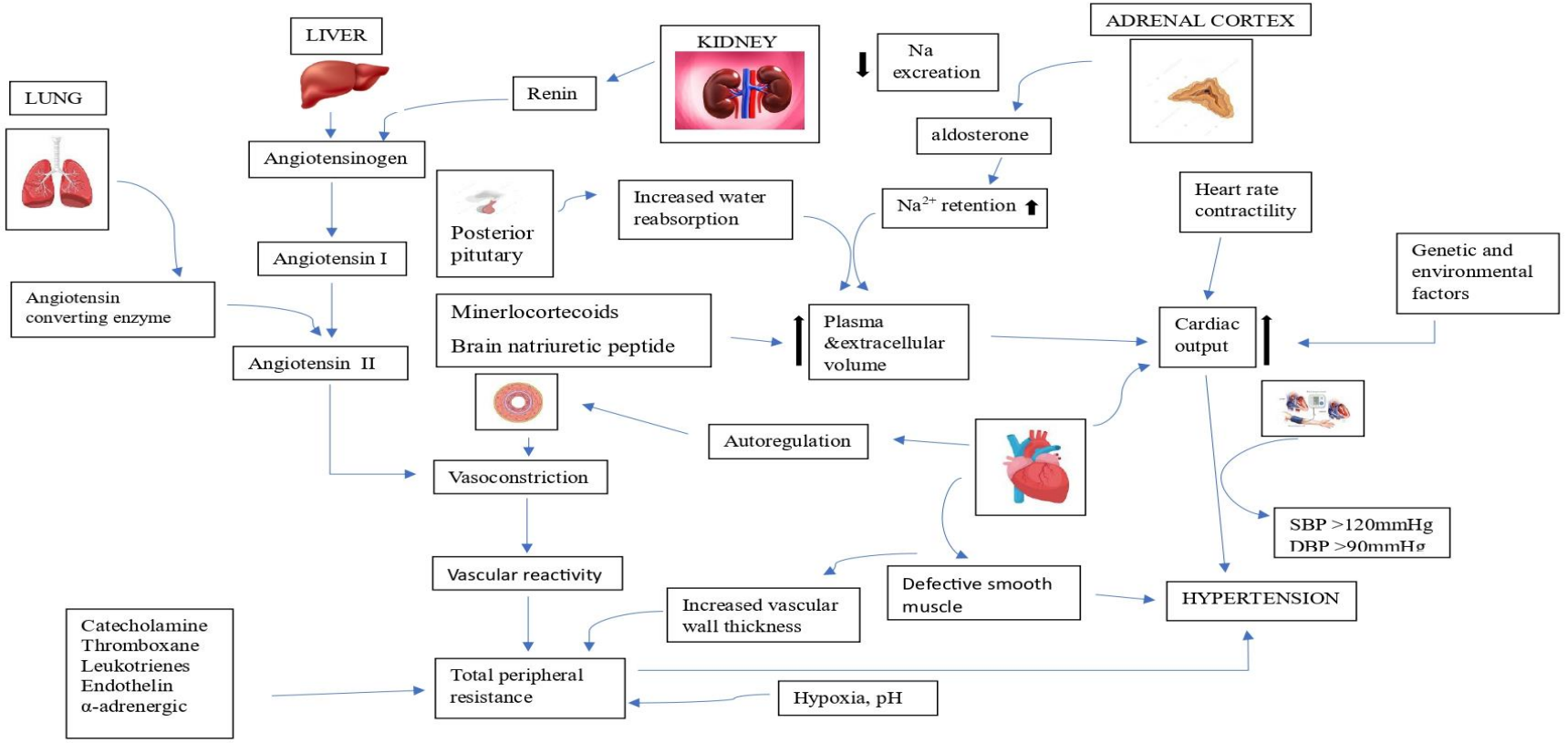

Fig.1 Pathophysiology of hypertension

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4. PRE-CLINICAL MODELS FOR HYPERTENSION

Based on the etiology of hypertension, commonly used animal models can be divided into primary and secondary hypertension groups. Only a small portion of hypertension in humans is due to secondary causes, which are typically modelled by treatments such as renal artery blockage. Spontaneously hypertensive rats (SHR) are genetic models of hypertension that closely mirror the most prevalent type of the disease in humans, known as primary hypertension.

Table 1: *In-vivo* models of Hypertension

SL NO	PRE-CLINICAL MODELS	SUB MODELS
1	Reno-vascular hypertension[20]	➢ Model of 2 Kidney 1 Clip ➢ Model of 1 Kidney 1 Clip ➢ Model of 2 Kidney 1 Clip
2	Hypertension originating from renal parenchyma	➢ Salt-Induced Model with Reduced Renal Mass
3	Pharmacologically induced hypertension	➢ Glucocorticoid induced model ➢ Deoxycorticosterone Acetate-Salt (Mineralocorticoid) induced model ➢ Pithed rats blood pressure model ➢ Hypertension induced by diet ➢ Hypertension induced by cold ➢ L-NAME induced rat model
4	Genetic Models of hypertension	➢ Gene modified rat models ➢ Gene Knockout models

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		➢ Transgenic strains ➢ Inbred rat model
5	Ecological Models of hypertension[21]	➢ Light flashing model ➢ Loud noises model ➢ Rotating enclosures model

RENOVASCULAR HYPERTENSION

a) Model of 2 Kidney 1 Clip

Male SD rats aged one week and weighing between 160 to 180 grams are tested in the experiments. The protocols adhere to the guidelines outlined in the guide for the care and use of laboratory animals. The rats are housed in a controlled climate with 12 hours of darkness and brightness. They received regular food & unlimited access to tap water.

In this model sodium pentobarbital (50 mg/kg i.p.) is used to induce anaesthesia during a retroperitoneal flank incision in rats. To cause Renal-vascular hypertension, a U-shaped silver clip with an internal diameter of 0.2 mm is placed on the right renal artery, exposing and partially occulting it. The prominent major renal nerve bundle is carefully avoided from being severed. Rats with normal blood pressure received a comparable surgical procedure without any cutting. The rats are then maintained in identical environments. The study criteria for hypertension are a systolic blood pressure (SBP) of 160 mmHg. Renal sympathetic denervation was administered to 46 out of 53 rats (86.8%) that satisfied the blood pressure criteria.[22, 23]

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b) Model of 1 Kidney 1 Clip

Wistar rats weighing between 230 to 260 grams are housed in a controlled climate with 12hrs of darkness and brightness. 3 days before the experiment the animals are given unlimited access to food and drink.

One "clip" and one "kidney" in animals (1K1C group), (Gold Blatt et al.1934) created Reno-vascular hypertension by partially constricting the major left kidney's artery with a silver clip (gap of 0.15 mm), which is followed by unilateral nephrectomy using a method Schaffner burg adapted for small animals. Another group of animals (sham group, n=16) are used the same sham operation, which involved dissecting the left renal artery without implanting a silver clip and without performing a contralateral nephrectomy. Following surgery, the 1K1C hypertensive and sham animals are kept in a room with controlled temperature and twelve hours of darkness and brightness and their cages have free unlimited tap water. Nine days following surgery, the experimental treatments are initiated to induce hypertension.

The animals underwent instrumentation with femoral venous and arterial catheters which are infused with heparinized saline (500 UI/mL) and these catheters are then externalized through the back on the eighth day, all while the animals are under tribromoethanol anaesthesia (250 mg/kg, i.p.). A pressure transducer (AD Instrument) is used to capture data 24 hours after the surgical procedures and as well an amplified signal (AD Instrument) is sent to a data spending board (AD Instruments - Power Lab 8/30). Every animal included in the research study has its cage. The arterial pulse pressure is used to compute the mean arterial pressure (MAP) and heart rate in cardiovascular health. The rats are placed in a quiet room and given at least thirty minutes to get used to their surroundings.[24, 25]

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HYPERTENSION ORIGINATING FROM RENAL PARENCHYMA–SALT-INDUCED MODEL WITH REDUCED RENAL MASS

Practically, loss of renal function is the most frequent secondary cause of hypertension. The reduced renal mass model, which is most frequently examined in rats and dogs and it, is the animal model that resembles this clinical illness the most. 85% decrease in kidney mass is necessary in this model. This is accomplished by surgically removing two-thirds of the remaining kidney after a unilateral nephrectomy. This level of renal mass decrease alone causes a negligible rise in blood pressure in contrast to normal, sham-operated control animals. The addition of too much salt to food or drink might cause blood pressure to rise even more. Plasma renin activity is modest and the HTN is reliant on salt lower renal mass salt-induced paradigm. However, in this model, BP is lowered by RAS inhibition using ACE inhibitors or angiotensin receptor blockers. This seeming paradox can be explained by the way that anti-RAS medications inhibit the tissue RAS, as well as how the reduction of the central nervous system (CNS) angiotensin II effects reduces sympathetic nervous system (SNS) activity. [20]

HYPERTENSION INDUCED BY PHARMACOLOGICAL ACTIVITIES

a) Hypertension induced by Deoxycorticosterone Acetate-Salt (Mineralocorticoid)

Model

It is believed that mineralocorticoid-induced hypertension results from the steroid's ability to retain sodium, which raises plasma and extracellular volume. In rats, unilateral nephrectomy and salt loading both intensify the hypertensive impact. Strong people can be made unconscious using ether. 250-300g of SD rats was taken for study. A side cut has been made to undergo left kidney removal. For four weeks, the rats get two weekly administering 20 mg/kg subcutaneous desoxycorticosterone acetate in olive oil. Replaced with a 1% NaCl

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solution, drinking water is used. Blood pressure starts to rise after one week, reaching systolic values ranging between 160 and 180 mmHg after four weeks. [26, 27]

b) L-NAME-induced hypertension

Male SD rats, aged 6~7 weeks and weighing 193±9.5 g, are utilized. Every animal is kept in a room temperature environment with a 12 hrs, darkness and lightness. They have been given a regular chow diet. Following for few days of acclimatization, the experimental animals are split into subsequent trial groups randomly. The rats in the L-NAME-treated group received a dosage of L-NAME (40 mg/kg/day, orally) for three weeks, whereas rats in the normal control group are administered olive oil (as a carrier). Subgroups of the animals treated with L-NAME are randomly assigned into different treatment categories.

Every week, rat heart rate and elevated blood pressure are calculated by using CODA, an automated non-invasive blood pressure monitor that uses volume pressure to estimate tail blood pressure. Rats are placed in a restrainer with their tails exposed upon the hot surface. A volume pressure-recording device and an occlusion device are positioned towards the end of the tails. The digital values of the heart rate, as well as the diastolic and systolic (SBP) stages, are noted. Every rat is measured for 20 cycles and the greatest and lowest readings are eliminated. The same individual took all the measurements at the same time of day, in the same calm setting, to reduce the effects of stress on blood pressure changes. [28, 29]

c) Pitched rat blood pressure model

The pithed rat paradigm lacks neurogenic reflex control, potentially altering the main pharmacological action. It is commonly used to evaluate how medications influence the cardiovascular system. Halothane is used to anaesthetised the animals. The carotid artery is cannulated for blood sampling and monitoring purposes. The animal's trachea is cannulated, and a ventilation pump is utilized to maintain artificial breathing (at 60 cycles per minute). In addition, the jugular vein is cannulated to provide the test drug. Pitching is a treatment that

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entails passing a steel rod with a diameter of 2.2 mm and length of 11 cm through the orbit and foramen magnum, as well as down the entire spinal canal. To increase the oxygen content of inspired air, attach a T-piece to the air input of the ventilation pump inspired air becomes more oxygen-rich. After 30 minutes of pitting, a blood gas analyser extracts 0.3 mL of blood from the carotid cannula to measure pO_2, pCO_2, pH, and bicarbonate content. Blood pressure and cardiac frequency are monitored through the carotid artery. Blood pressure and heart rate are recorded via the carotid artery. The first dosage response curves for phenylephrine (0.1-30 g/kg, intravenously) and BHT 920 (1-1000 g/kg, intravenously) are recorded. The agonist dose-response curves are repeated 15 minutes after the test medicine is administered intravenously. The agonist curve is obtained to determine blood pressure response. The dose-response curves are plotted using logarithmic probit scales. The dose-response curves are used to compute the potency ratio.[30]

GENETIC MODELS OF HYPERTENSION

a) Inbred Rat Models

Because of the small size of rats, simplicity of handling, breeding, and relatively cheap cost, the rat remains the primary animal used in the great bulk of contemporary research on experimental hypertension. In the previous ten years, a great deal of effort has gone into mapping the rat genome from a genetic perspective. The rat genome map now has a genetic marker density that is comparable to the mouse genome map. The challenge of gene manipulation has been a drawback for the rat, compared to the mouse, which is its primary rival as the primary animal model in hypertension research. It is frequently possible to modify, add or remove genes of interest in mice (a process known as knockout or knocking), and then to observe any changes in structure and function. In the rat, these potent instruments for studying the significant role of genes in wellness and illness are the only smart part

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available. Because of this one key benefit over the rat along with its lower weight and quick mating cycle, researchers have created novel techniques that allow for the assessment of cardiovascular factors in mice, such as blood pressure. These are still in the early phases of progress and only a small number of centres have acquired the technological know-how required to regularly employ mice as research instruments in hypertension. Furthermore, there is currently a lack of knowledge on the degree to which the physiology and pathophysiology of mice are similar to those of humans, making them a suitable model for use in experiments involving human hypertension.[31]

b) Genetically modified models of Hypertension

There are numerous genetically engineered models of Peripheral artery hypertension (PAH). The most popular models are fawn-hooded rats subjected to prolonged hypoxia or mice overexpressing S100A4, IL-6, TNFα, or 5-HTT (also known as SERT). These models are useful for studying the mechanisms that lead to the formation and progression of hypertension. However, they lack all clinical features of BP and, in the case of fawn-hooded rats, develop systemic hypertension. Other animal models of hypertension, including smoke-induced and bleomycin-induced fibrosis, should be considered. These milder hypertension models can provide insights into the cellular and molecular factors behind elevated blood pressure. Animal models that combine multiple insults, such as SU5416/chronic hypoxia or monocrotaline and pneumonectomy, can create hypertension with pathophysiology more closely linked with the human situation. However, an appropriate clinical model is still unknown. Researchers should use multiple animal models to better understand the pathophysiology and find a therapeutic drug that can reverse PAH in people.[32]

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Transgenic Model

Furthermore, the ability to specifically insert genetic structures and then breed mutant species has opened up new possibilities for hypertension research. The transgenic rat, created by introducing the entire mouse Ren2d gene, was the first of its kind. This led to the development of a hypertensive animal that is highly responsive to RAS inhibition and whose hypertension and subsequent organ damage largely depend on increased local angiotensin II production. Other transgenic models are available in both mice and rats, where the introduction of renin and human angiotensinogen led to increased blood pressure. The latter strain is characterized by early death and severe hypertension.

A small subset of the numerous cardiovascular system components studied in transgenic rats have successfully resulted in hypertension models. The knockout models, in which the genes for NO-synthesis and ANF are absent, are noteworthy. While the loss of the type a receptor for ANF led to salt-independent hypertension, the loss of ANF caused salt-sensitive hypertension. These results highlight a crucial point: the absence of protective factors can also result in elevated blood pressure. Hypertension can be generated by the addition of specific variables.[33]

The SHR strain developed in Kyoto, Japan, from a hybrid between an outbred Wistar male rat with naturally raised blood pressure and a female with mildly elevated blood pressure. They proceeded with further mating between siblings, selecting for animals exhibiting systolic blood pressure greater than 150 mmHg. As adults, the animals develop hypertension on themselves. The SHR is commonly utilized in studies as a rat model for primary or essential hypertension. This strain, including the stroke-prone SHR, has been used to study stroke, vascular function, autonomic regulation, renal function, therapeutic treatments, and primary hypertension genetics.[34]

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ECOLOGICAL MODELS OF HYPERTENSION

a) Loud noise induced hypertension model

The short and long-term consequences of noise exposure, along with noise-induced annoyance, can lead to detrimental effects such as hearing impairment and disruptions in sleep, interactions, and daily activities. The later effect is associated with an increased risk of high blood pressure along with other heart diseases. The World Health Organization (WHO) estimates that every year in Western European countries, noise-induced heart failure leads to 61000 DALYs which are destroyed, noise-induced sleep problems 903 000 DALYs, and noise-induced irritation 587 000 DALYs, the latter of which reduces the level life span as well as raises impairment.[35]

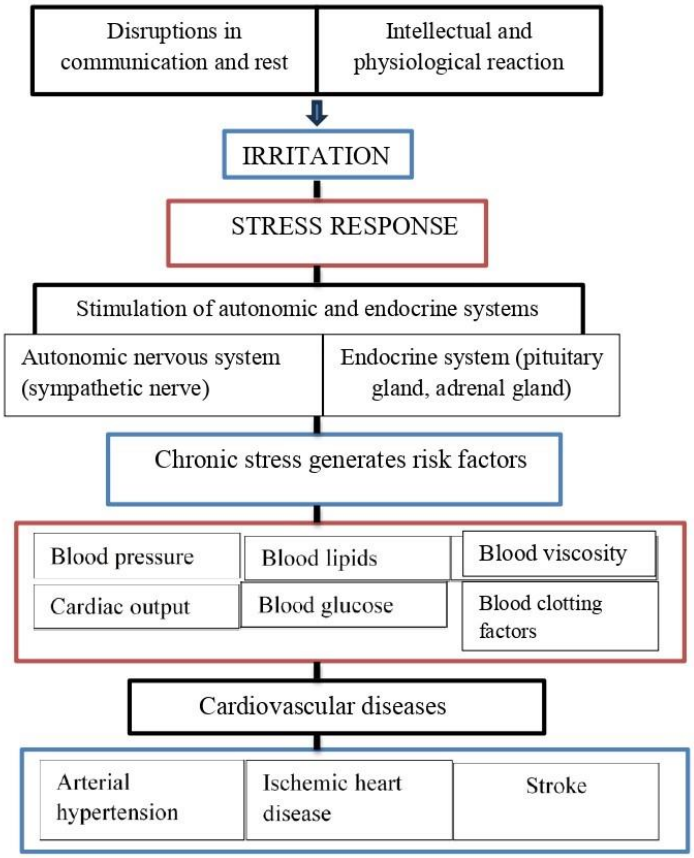

Fig.2 Loud noise induced hypertension

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***In-vitro* models**

1. Endocrine-dependent relaxation and alpha 2-adrenoceptors in canine big arteries
2. Monocrotaline induced Pulmonary Hypertension
3. ACE Inhibition in Guinea Pig ileum
4. Beta adrenal receptor activity
5. Antagonism of endothelin receptors in porcine isolated hearts.[36]

Endothelin receptor antagonistic activity in isolated pig hearts

There is proof that endothelin (ET) plays a role in the pathogenesis of cardiovascular disease. The isolated pig coronary artery is employed in this model because the soft tissue of the capillaries includes the ET_A binding sites. Strong, protected contractions are induced in isolated blood vessel strips by ET. Studies conducted *in vivo* and *in vitro* have demonstrated that endothelin peptides increase blood pressure. Six domestic, cross breed, 12-week-old female pigs weighing 30 to 40 kg are being examined. The pigs are sedated with xylazine (0.03 mg/kg/min) and ketamine (0.2 mg/kg/min). A left thoracotomy reveals the heart. Porcine hearts are used to isolate the left anterior descending coronary arteries. They are washed first and then the fat and connective tissue are extracted. Spiral strips, 10 mm lengthy and 1 mm broad are removed from the endothelium-denuded arteries. To remove the vascular endothelium, gently remove the innermost layer of the spiral rings using filter paper. Every sheet is immersed in a Krebs-Henseleit solution that has been agitated with 95% O_2 and 5% CO_2 at 37 °C. 50 mM KCl is used to achieve isometric contraction once the isolated preparation has stabilized. ET-1 concentration reaction curves are produced by injecting ET-1 cumulatively. Twenty minutes before the administration of ET-1, the endothelin receptor antagonist/test drug is administered to the tissue bath, and has concentration-response curve is recorded. Schild plot analysis provides the values, slope, and pA.[37]

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Monocrotaline-induced pulmonary hypertension

Rats are given monocrotaline, a hepatotoxic and pneumotoxic drug, to cause pulmonary hypertension. This alkaloid, called pyrrolizidine, is extracted from *Crotalaria spectabilis*. A single dose causes cardiac hypertrophy, cardiac failure, and progressive pulmonary hypertension. Additionally observed are ultrasound changes such as endothelial cell destruction and fragmentation, perivascular swelling, red blood cell extra vision, and muscularization of the pulmonary blood vessels. When rats are given monocrotaline, they may develop significant cardiac hypertrophy, oedemas, and pleural effusion.

One week of the test medication is given to SD rats subcutaneously prior to getting a single dose of 100 mg/kg monocrotaline. Four, seven, or fourteen days after the animals are slain; their CVS and respiratory system are removed from their thoracic cavities. Calculating is done on the left lung & ventricle. Additionally isolated are their intra-pulmonary artery, right extra pulmonary artery, main pulmonary artery, and pulmonary arterial segments. Every vessel is hung between stainless steel hooks in tissue baths that are filled with Krebs-Hensleit buffer that has been aerated at 37 °C with 95% oxygen and CO_2. After the experiment, parts of vessels are weighed, measured for dimensions, and blotted.

Tissue weight and diameter are used to calculate the cross-sectional area of an artery. Arteries are forced to reduce to KCl ($6X10^{-2}$ M) afterwards one hour. In the context of applied force, changes in isometric force are monitored using force displacement transducers on a polygraph. In pulmonary arteries, responses to contractile and relaxant agonists are quantified. In pulmonary arteries, contractile and relaxant agonist responses are measured. Graphs are plotted for continuous concentration-response curves to KCl, angiotensin II and adrenaline. Contractions have been defined as force produced per cross-sectional area and active tension development. The plotting of contractile and relaxation responses is based on

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the intensity of the inverse slope of the agonist. That grouped data t-test is employed to compare variations in the mean responses.[38]

Table 2: Advantages and limitations of models

SL. NO	MODELS	ADVANTAGES	LIMITATIONS
1	Model of 2 Kidney 1 Clip	✓ Mimics human disease ✓ Focus on RAS and drug testing	✓ Surgical Skill Required ✓ Species Differences
2	Model of 1 Kidney 1 Clip	✓ Simple setup model	✓ Single kidney focus ✓ Limited Reno-vascular function
3	Model of 2 Kidney 1 Clip	✓ Consistent Blood Pressure Increase ✓ Vascular and Cardiac Effects due to sustained high BP	✓ Surgical Skill Needed ✓ Limited to RAS Pathway
4	Salt-Induced Model with Reduced Renal Mass	✓ Testing of Salt-Restriction Therapies ✓ Study of Salt Sensitivity	✓ Simplified Pathophysiology ✓ Potential for Severe Kidney Damage
5	DOCA Salt induced model	✓ Studies Hormonal Influence ✓ Simple and Reliable	✓ Non-Physiological in hypertension ✓ Kidney Damage Risk
6	L-NAME induced model	✓ Studies Nitric Oxide Role ✓ Helps to study vascular function and its impact on blood pressure regulation.	✓ Lacks Multifactorial Complexity ✓ Species Differences
7	Pitched rat model	✓ Useful for long-term studies of chronic hypertension measurement	✓ Surgical complexity
8	Inbred rat model	✓ Consistent genetic background, which reduces variability in experimental results. ✓ Disease Modelling	✓ Limited Genetic Diversity
9	Gene modified rat model	✓ Targeted Genetic Study	✓ Complex and Costly ✓ Limited to Specific Mutations
10	Transgenic model	✓ Specific Gene Expression ✓ Testing of gene-based therapies and interventions	✓ Unintended Effects ✓ Developing and maintaining transgenic animals is technically challenging and costly.
11	Loud noises model	✓ Provides a model to explore the physiological and psychological mechanisms linking stress to hypertension. ✓ Useful for studying how chronic exposure to loud noises can induce high blood pressure.	✓ The model may involve uncontrolled stressors beyond just noise, complicating the study of hypertension.

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12	Endothelin receptor antagonist activity in isolated pig rats	✓ Understanding Vascular Function ✓ Alpha 2-Adrenoceptor Role	✓ Complex Interactions ✓ Limited Scope
13	Monocrotaline induced pulmonary hypertension	✓ Mimics Human Disease ✓ Simple Administration	✓ Non-Specific Effects ✓ Severe Disease Progression
14	Beta adrenal receptor activity	✓ Cardiovascular Insights ✓ Drug Development	✓ Complex Interactions ✓ Limited to Sympathetic Pathway

5. MONITORING HYPERTENSION IN PRE-CLINICAL MODELS

Non-invasive technique

An accurate BP curve and empirical BP values can be evaluated thanks to the development of continuous non-invasive blood pressure monitoring techniques in recent years (only with direct BP measurement). The arterial application tonometry or the volume clamp methods are the two different types upon which the constant non-invasive measurement principles are based.[39]

a) Tail cuff method

This device is a commonly used method now used to monitor blood pressure in conscious rats and mice (8–12). One benefit of the tail-cuff approach is that it is non-invasive. The method depends on keeping the tail's blood flow at a minimum therefore every biological, medicinal, or ecological component that affects the flow of tail blood will also impact the blood pressure reading. More additional studies into the accuracy of the tail-cuff technique of BP monitoring in mice are required to determine its ultimate worth.[40]

Select the animals to repair the device according to the manufacturer's instructions. Reset the apparatus as needed to detect the body weight of the rat. Injection of 30 mg/kg sodium pentobarbital intra-peritoneal acclimatizes the animals in an incubator at 37 °C for 10

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min before the measurements. Lay the rat on the equipment table and fit the cuff around the tail of the rat. TA11 PA-C40 rat blood pressure implant pumps the cuff using a hand bulb sphygmomanometer till it reaches a pressure of approximately 30 mmHg higher than the systolic pressure. Gradually compress the cuff at a speed of 3-4 mmHg/s, checking the pulse outputs on the oscilloscope recorded the data on the oscilloscope when the pulsations reoccur during compression. Record the readings as the systolic pressure restart the procedure at least three times at 3 min period and let the animal back to normal.[41]

b) Electrocardiography

A non-invasive technique for recording ECGs involves putting rats in a cotton jacket with two electrodes sewn to the inside. Rat's skin in the anterior thoracic region needs to be shaved before donning the coat. Rats that are conscious and in plastic restraints are used for measurements (Pereira-Junior et al. 2010). This method has several benefits over telemetry, such as being non-invasive, measuring in conscious animals, and being substantially less expensive. However, the method's main drawbacks are restraint stress and challenges with aligning the electrodes in the same spot on several rats. A further technique involves non-invasively recording the ECG of conscious rats kept in a tunnel-like restraint. This method involves placing the rat's paw on ECG sensors buried in the tunnel floor. Up to six lead ECGs, lasting 30 to 60 min, can be acquired after a brief adaption time.[42]

Invasive method

It is generally accepted that taking an invasive blood pressure reading (IBP) is the gold standard. IBP gives a clear picture of how the experimental products affect the heart and blood vessels. To find out how a product may affect the cardiovascular system, it is imperative to record the IBP in rats as part of the first screening process. IBP is the arterial blood pressure directly recorded in any artery such as the radial, femoral, or brachial artery using a cannula (saline-filled catheter).[6]

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a) The carotid arterial cannualation in rats

The rats utilized in this investigation are housed in regulated environments and received unlimited rat feed and water *ad libitum.* The test animals, 10 rats of either sex are chosen for the protocol testing. All experimental animals are clinically examined and are weighed prior to the trial. Inhalator anaesthesia has been employed using Isoflurane (ISO) with a Single Animal System. General anaesthesia has been given in the infusion chamber with (3-5%) ISO in combination with oxygen, sustained on the mask with (1-1.5%) ISO. Each person received Tramadol for analgesia 20mg/kg. Animals are put in anterior recumbence on an electrical pillow to avoid hypothermia during the trial & 5ml syringe is positioned beneath the neck for improvement of cervical stimulation. Surgical carotid cannualation in the ventral cervical area has been performed on rats. The hair is clipped and the wound location is clinically prepared using Betadine and Chlorhexidine. The rat is covered using sterile fabrics to safeguard the surgical area. Using a 10-blade, 2cm slice of skin is made on the ventral middle line of the neck on the supra–clavicular portion. A blepharostat is used to stretch the skin. Exercising a Metzenbaum scissor and soft forceps the left carotid has been revealed by gentle analysis of the muscular layers and the omohyoid muscle is precisely sliced for a better exposure of the capillaries. Through an ophthalmologic needle holder, a proximal ligation has been placed on the carotid artery to along with the vagal nerve, and a 4.0 poly filament wire has been utilized to insert a loose one proximally. The carotid is being gently pulled up using a Graham hook. An ordinary intravenous cannula (24G) has been placed and bounded with the proximal suture, carefully not to impede the blood flow through the carotid cannula. A blood pressure measurement device (produced by Edwards Life Sciences) calibrated to the level of the right atrium is connected to the arterial catheter with an intravascular elongation, filled with normal saline solution (0.9%), and to the dragger absolute delta monitor. The catheter is washed with 0.1 ml of 0.9% normal saline

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every 30 minutes to avoid blood clot formation. All rats are connected to a 0.9% saline solution used for the catheter has been washed to avoid blood clotting. The skin is closed with a 4.0 wire in basic points. Variations in arterial pressure are conveyed by fluid-filled catheters, which transform into electrical signals depicted by hemodynamic waveforms. Every 30 minutes, the MAP of each patient is recorded for eight hours while they are kept under anaesthesia. The first recorded is considered the control result. At the end of the experiment, all the rats are sacrificed with a high dose of aesthetic. The consistencies of the rats are tested through standard deviation of the average weight and it is confirmed by the coefficient of variation result. It is also determined if there have been statistical variations between the females and males regarding the weight by t-test. The results collected for MAP are processed with ANOVA, comparison with the control results through the significant limit of differences (SLD) for p=5%; 1%; 0.1% and multiple comparisons by Duncan test.[43]

b) Caudal ventral artery by monitoring elevated blood pressure in rats

Male SD rats of 9-12 weeks aged; 276-499 g with normal blood pressure are taken. 12 hours of lightness and darkness with controlled environmental conditions like room temperature and humidity is maintained. Water and pelleted food are freely available to all of the rats. During the procedure, the inhaled anaesthetic is carefully regulated based on the Common Carotid Artery (CCA) BP and heart rate to keep each animal pain-free. Throughout surgery, the animals' body temperatures are kept between 36.5 and 36 °C. Within the animal infrastructures of Jokey University School of Medicine, the operation is held inside an integrated surgery centre equipped with digital subtraction angiography for experimental animal research. A combination of butorphanol tartrate (0.5 mg/mL), midazolam (0.4 mg/mL) & medetomidine hydrochloride (0.03 mg/mL) is induced intraperitoneally with rate of 5 mg/kg to induce anesthesia16, 18–20. The rodents are then given a 16-gauge catheter (Terumo, Tokyo, Japan) for endotracheal inhalation. Atipamezole HCl (0.7 mg/kg) has been

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administered intraperitoneally to counteract the outcomes of medetomidine after intubation. After intubation, an animal ventilator and 1-3 percentage Isoflurane are used to maintain anaesthesia. Vital sign monitoring (temperature, blood pressure, and SpO_2) is done in real-time with the Life Scope VS. A multipaned heater is used to maintain body temperature once ventilation and circulation have stabilized. A tiny animal probe that is put into the oesophagus is used to measure the body temperature, which is suitably maintained between 36.5 and 36.3 °C.

ABP measuring probes are also invasively implanted in the CVA and CCA. The rat is first put in the supine posture and had Povidone-iodine applied to the skin of its tail. Then, to measure blood pressure, a 24-gauge catheter is properly placed within the CVA. The arterial line introducer is attached to the catheter once the catheter's backflow is verified. After confirming that the arterial waveform could be seen on the monitor, heparinized physiological normal saline is used to flush the catheter. Here rat's neck has been made hyperextended by placing a pillow beneath its shoulders, and Povidone-iodine is applied to the skin of the neck. A cut is made across the neck's midline. The avascular plane is penetrated, deepening the incision. By removing surface tissues to the left across the sternohyoid muscle's location, the left CCA has been made visible. The left CCA's sheath is bluntly surgery to reveal the CCA where a vagus nerve entered the CCA laterally a 24- gauge is inserted. The catheter is attached to the arterial line introducer once the backflow from the catheter is verified. The catheter has been washed with heparinized physiological normal saline and then secured in position with a silk knot after a waveform appeared on the monitor. Gauge catheter is then introduced in the proximal direction of the CCA after 4-0 silk knot had been wrapped approximately its distal and also proximal regions.[44]

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6. CONCLUSION

Managing hypertension is crucial for maintaining a healthy lifestyle. Preventing high blood pressure through healthy habits such as consuming a diet rich in fruits and vegetables and engaging in regular physical exercise is essential. The pathophysiology of hypertension involves multiple factors, including neuronal, endocrine, and renal effects, all of which play a critical role in blood pressure regulation. Accurate measurement of elevated blood pressure is indispensable in diagnosing and managing hypertension, which is associated with significant health risks. Various animal models, including genetic, transgenic, and environmental models, represent different aspects of human hypertension, offering valuable insights into the disease. These models are vital for preclinical research, with reliable methods for measuring rodent blood pressure being a key technology in these studies. While lifestyle modifications remain the first step in preventing and managing hypertension, it is important to acknowledge that hypertension is a chronic condition that requires on-going management. Looking ahead, future advancements should focus on the development of accurate and non-invasive devices for blood pressure measurement. Although there are numerous effective and well-tolerated antihypertensive medications available today, further progress is needed to optimize their use, either individually or in combination. Continued research in this field will help refine treatment strategies and improve outcomes for individuals with hypertension.

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Conflicts of Interest

The authors declare no conflict of interest

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ABBREVIATIONS:

HTN – Hypertension

CVD – Cardiovascular Diseases

BP – Blood Pressure

JNC 8 – Eighth Joint National Committee

AHT – Antihypertensive Therapy

IBP – Invasive Blood Pressure

PAD – Peripheral Artery Disease

NO – Nitric Oxide

CKD – Chronic Kidney Disease

SHR – Spontaneously Hypertensive Rats

1K1C – 1 Kidney 1 Clip

2K1C – 2 Kidney 1 Clip

SBP – Systolic Blood Pressure

RAAS – Renin Angiotensin Aldosterone System

ACE – Angiotensin Converting Enzyme

MAP – Mean Arterial Pressure

CNS – Central Nervous System

SNS – Sympathetic Nervous System

ANF – Atrial Natriuretic Factor

L-NAME – L Nitro Arginine Methyl Ester

WHO – World Health Organization

ET – Endothelin

ED - Erectile dysfunction

ECG – Electrocardiography

ISO – Isoflurane

SLD – Significant Limit of Differences

CCA – Common Carotid Artery

CVA – Caudal Ventral Arteries

DASH – Dietary Approaches to Stop Hypertension

AT 1 – Angiotensin 1

ABP – Ambulatory Blood Pressure

PAH – Peripheral Artery Hypertension

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