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**Pharma Research Library**

**International Journal of Current Trends in Pharmaceutical Research**

**2013, Vol.1 (2): 144-152**

**ISSN 2321-3760**

**Review Article**

Pharma Research Library

# A Conceptual Overview of Hypertension with Special Consideration to Its Etiological & Clinical Classification, Pathophysiology and Treatment

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## Abstract

Cardiovascular diseases are one of the life threatening diseases of mankind and hypertension is the most common cardiovascular disease, which requires constant monitoring. It is well known that hypertension is a major factor for congestive cardiac failure and coronary artery disease. Elevated arterial pressure due to hypertension causes pathological changes in the vasculature and hypertrophy of the left ventricle. As a consequence, hypertension is the principal cause of the stroke, leads to disease of the coronary arteries with myocardial infarction and sudden death, and is a major contributor to cardiac failure. It is very much essential to control the hypertension and maintain sufficient blood circulation to heart to reduce the morbidity and make the patient to lead a near normal life. Control of hypertension reverses the risk of congestive cardiac failure; Recommendations as to forms of treatment regimens to be adopted including non pharmacological, monotherapy and appropriate combination therapy discussed exhaustively.

**Key words:** cardiovascular disease, Hypertension, elevated arterial pressure, pathological Changes, Monotherapy, Combination therapy

## Introduction

The World Health Organization describes hypertension as the number one risk factor for mortality, as worldwide annually 7.5 million deaths (13% of all deaths) are attributable to high blood pressure (BP)-related diseases, particularly cardiovascular diseases, and was ranked 13th in the leading global causes of death for all ages. Hypertension is a major risk factor for cardiovascular diseases, including heart failure, coronary heart disease, peripheral artery disease and stroke. Hypertension is often referred to as the 'silent killer', as its presence is usually symptomless [1,2].

**Blood Pressure**

Blood pressure is the lateral pressure exerted by blood on the vessel walls while flowing through it. The term blood pressure refers to arterial blood pressure. Arterial blood pressure is expressed in four different terms-

1. Systolic pressure
2. Diastolic blood pressure
3. Pulse pressure
4. Mean arterial pressure

**1. Systolic blood pressure-** is defined as the maximum pressure exerted in the arteries during systole of the heart. The normal systolic pressure is 120mmhg. It ranges between 110 to 140mmhg.

**2. Diastolic blood pressure-**is defined as the minimum pressure in the arteries during diastole of the heart. The normal diastolic pressure is 80mmhg. It varies between 60 to 80mmhg.

**3. Pulse pressure-** is the difference between the systolic pressure and diastolic pressure. Normally, it is 40mmhg.

**4. Mean arterial blood pressure-** it is the average pressure existing in the arteries. It is not the arithmetic mean of systolic and diastolic pressures. It is the diastolic pressure plus one-third of pulse pressure. Normal mean arterial pressure is 93mmhg [2,4].

**Historical background**

Blood pressure was first measured in a mare in1733, by Stephen Hales with a long tube of about 9 feet length. Poiseeuille reduced the length of the tube to one foot and used mercury to balance the column of blood in 1847. Ludwig placed a float on the top mercury column and made continuous recording possible. The introduction of rubber tubing, anaesthesia and manometer enables the accurate measurement of blood pressure. The importance of hypertension was recognized in the 1950's, the Indian Snakeroot (Rauwolfia) was employed for centuries by Indian physicians before Reserpine was extracted from the root and found to be spectacularly effective in the treatment of hypertension. The Chinese had some understanding of circulation. Hung Ti, in 2500 BC stated, "The blood current flows continuously in a circle and never stops.., if too much salt is used in food, the pulse hardens". The Egyptian around 2000 BC believed that the pulse was the speech of the heart and used bloodletting and a wide range of drugs. Hippocrates (460-370 BC), the Father of Medicine, changed the destiny of medicine by raising it to the status of a science. He stressed on the complete systemic examination including the pulse. Herophilus in 300 BC used a water clock to time the pulse and noted the systolic and diastolic phases of pulse. Blood pressure is altered in physiological and pathological conditions. Systolic pressure is subjected for variations easily and quickly and its variation occur in a wider range. Diastolic pressure is not subjected for easy and quick variations and its variation occurs in a narrow range [1,8,13].

**Physiological Variations**

**Age**- blood pressure rises with age. The systolic pressure in different age-

In new born - 40mmhg
After 15 days - 70mmhg
After 1 month - 90mmhg
At puberty - 120mmhg
At 50 years - 140mmhg
At 70 years - 160mmhg
At 80 years - 180mmhg

The diastolic pressure in different age;

At puberty - 80mmhg
At 50 years - 85mmhg
At 70 years - 90mmhg
At 80 years - 95mmhg.

**Sex-** in females, up to the period of menopause, the arterial pressure is low (up to 5mmhg) as compared to the males of same age.

**Build-**the pressure is more in obese persons than in lean persons.

**Diurnal variation-** in early morning, the pressure is slightly low. It gradually increases and reaches the maximum at noon. It becomes low in evening.

**Posture-**the diastolic pressure is slightly higher in the standing position. In the recumbent position the diastolic pressure is lower than in the sitting position.

**After meals-**the pressure is increased foe few hours after meals due to increase in cardiac output.

**Sleep-**the systolic pressure falls by about 15-20mmhg during sleep.

**Emotion or excitement-** It causes increase of systolic pressure.

**After exercise-**in strenuous exercise the systolicpressure rises and may reach even up to 180mmhg. In moderate exercise there is slight rise of systolic blood pressure [2,4].

**Pathological Variations**

The pathological variations of the arterial blood pressure are- Hypertension and Hypotension [8].

**Measurement of Blood Pressure**

Blood pressure was first measured in horse in 1733, by Stephen hales with a long tube of about 9 feet length. Later, poiseuille reduced the length of the tube to one foot and used mercury to balance the column of blood. In 1847, Ludwig placed a float on the top of mercury column and made continuous recording possible.

Blood pressure is measured by two methods-

1. Direct method.
2. Indirect method.

1. **Direct method-** the direct method to measure arterial blood pressure is employed only in animals. The animal is given suitable anesthesia, then the neck is opened and a tracheal cannula is inserted into the trachea. This tracheal cannula is connected to a respiratory pump, so that the respiration in the animal is controlled artificially toavoid any disturbance. The carotid artery is cannulated and connected to a mercury manometer. By using a kymograph, the blood pressure can be recorded continuously in the form of a graph.

2. **Indirect method-** the pressure may be measured without any surgical procedure, in this method commonly the pressure of the brachial artery is measured. The instrument used is known as sphygmomanometer. The blood pressure can be measured by three methods-

a) Oscillatory method.
b) Palpatory method.
c) Auscultatory method.

**a) Oscillatory method-** in this method a pressure cuff is wrapped over the brachial artery and the oscillations that are produced by the pulsations, are observed. The instrument is always kept at the heart level. When the cuff pressure is increased and raised above the systolic pressure, the oscillations disappear, but on releasing the pressure gradually, the oscillations become larger and prominent. The pressure head at which the larger oscillations are seen, is considered as systolic pressure. But on further release of pressure, the oscillations become smaller and disappeared. The pressure at which the oscillations just becomes smaller or disappears, is known as diastolic pressure.

**b) Palpatory method-**the instrument is kept at the level of the heart and the cuff is tied round the upper arm. Pressure is raised to 200 mm hg and then gradually released. When the pulse just appears at the wrist, the pressure is noted. This is systolic pressure. This method is not accurate. By this method the diastolic pressure cannot be determined.

**c) Auscultatory method-**this is the most accurate method to determine arterial blood pressure. After determining the systolic pressure in palpatory method , the pressure in the cuff is raised by about 20mmhg, the brachial artery is occluded due to compression. Now, the chest piece of the stethoscope is placed over the cubital fossa, and the pressure is released from the cuff. While doing so, seriesof sounds are heard through the stethoscope.

These sounds are known as korotkoff's sounds,which appear in four phases-

**First Phase-** sudden appearance of a clear tapping sound. This indicates systolic pressure. It persists while the pressure falls through 15mmhg.

**Second Phase-**the tap sound is replaced by a murmur persisting for another 15mmhg.

**Third Phase-**the murmur is replaced by a clear loud gong sound lasting for the next 20mmhg.

**Fourth Phase-**the loud sound suddenly becomes muffled and rapidly begins to fade.

This point indicates diastolic pressure [2,8,13].

**Definition of Hypertension**

Hypertension is the most common cardiovascular disease (CVDs). Hypertension is simply defined as persistently elevated arterial blood pressure (BP). According to Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) defines Hypertension as systolic blood pressure (SBP) $\geq$ 140 mmHg and a diastolic blood pressure (DBP) $\geq$ 90 mmHg for persons up to 60 years of age and for subjects with diabetes mellitus or familiar hypercholesterolemia and as a SBP $\geq$ 160 mmHg and a DBP $\geq$ 90 mmHg for persons of 60 years and older without diabetes mellitus or familiar hypercholesterolemia [1]. Elevated arterial pressure causes pathological changes in the vasculature and hypertrophy of the left ventricle. As a consequence, hypertension is the principal cause of stroke, is a major risk factor for coronary artery disease and its attendant complications myocardial infarction and sudden cardiac death, and is a major contributor to cardiac failure, renal insufficiency, and dissecting aneurysm of the aorta [8].

The World Health Organization reported that suboptimal blood pressure (SBP > 115 mmHg) is responsible for 62% of all cerebrovascular diseases and 49% of all ischemic heart diseases. In addition, suboptimal blood pressure is the number one cause of death throughout the Western world[8,15].

**Etiological Classification of Hypertension**

Hypertension is heterogeneous medical condition. In most of the patient it resulted from the unknown pathophysiologic etiology (essential or primary hypertension). While this form of hypertension can not be cured, it can be controlled Small percentages have a specific cause of their hypertension (secondary hypertension). There are many potential secondary causes that are either concurrent medical conditions or are endogenously induced. If the cause of secondary hypertension can be identified, hypertension in these patients potentially can be cured.

**A. Essential hypertension:**

Over 90% of individuals with hypertension have essential hypertension (primary hypertension). Various mechanism have been identified that may contributed to the pathogenesis of this form of hypertension, so identifying the exact underlying abnormality is not possible. In some families, the genetic factor may play an important role in development of essential hypertension. In future identifying individuals with these genetic traits could lead toalternative approaches to preventing or treating hypertension.

**B. Secondary hypertension:**

Fewer than 10% of patient have secondary hypertension, where either there a comorbid disease or a drug is responsible for elevating BP. In most of these cases, renal dysfunction resulting from chronic kidney disease or renovascular disease is the most common secondary cause. Certain drugs either directly or indirectly, can cause hypertension or exacerbate hypertension by increase in BP.

Both essential and secondary hypertension may be benign or malignant.

**Benign hypertension** is moderate elevation of blood pressure and the rise is slow over the years. About 90% patients of hypertension have benign hypertension.

**Malignant hypertension** is marked and rapid increase of blood pressure to 200/140mm Hg. Or more and patients have papilloedema, retinal haemorrhages and hypertensive encephalopathy. Less than 5% of hypertensive patients develop malignant hypertension and life expectancy after diagnosis in these patients is less than 2 years if not treated effectively [5,9,10,14].

| Drug Associated Hypertension | | | |
|---|---|---|---|
| **Prescription drug** | **Natural products** | **Food substance** | **Chemical Elements** |
| Corticosteroid | Cocaine | Sodium | Lead |
| ACTH | Nicotine | ethanol | Mercury |
| COX2 inhibitor | Phenyl | Liquorice | Thallium |
| Erythropoietin | Propanolamine | Tyramine, containing food if taking, amonoamine, oxidase inhibiter | Lithium |
| Antidepressant | analogues | | |
| Cyclosporine | Methylphenidate | | |
| Tacrolimus | Phencyclidine | | |
| | Ketamine | | |
| | Ergotamine | | |
| | Other ergot-containing herbal products | | |

**Clinical Classification of Hypertension** [6,7, 8,9,10,15]

Although hypertension is rise blood pressure above the normal clinical values, which can be mild to severe and therefore classified clinically as summarized below:-

| **Clinical Classification** | **Systolic (mm of Hg)** | **Diastolic (mm of Hg)** |
|---|---|---|
| Normal | <130 | <85 |
| Pre-hypertension | 130-139 | 85-89 |
| **Hypertension** | | |
| Mild stage (stage 1) | 140-159 | 90-99 |

| | | |
|---|---|---|
| Moderate (stage 2) | 160-179 | 100-109 |
| Severe (stage 3) | 180-209 | 110-119 |
| Very sever (stage 4) | >210 | >120 |
| Malignant hypertension | >200 | >140 |

**Pathophysiology of Hypertension**

The initiating factor causing hypertension is still unknown. In chronic hypertension, elevated blood pressure is maintained by an increase in total peripheral vascular resistance while cardiac output remains normal under most conditions. This observation stresses the importance of factors regulating vascular tone in the pathogenesis of high blood pressure. In hypertension, the function of one or more controlling systems regulating peripheral vascular resistance is impaired [1].

The controlling systems governing total peripheral / vascular resistance include:-

1. The autonomic nervous system, which innervated the smooth muscle cells of the blood vessel wall.
2. The kidney which adjusts salt and water excretion and produces pressure and depressor hormones.
3. The adrenal gland which secretes the hormones regulating water and salt metabolism and vascular tone.
4. Blood vessel wall itself, which contributes to its own responsiveness by morphological adaptation, changes in sensitivity and density of receptors of its smooth muscle by modulator effects of endothelium derived vasoactive substances [5].

**Sympathetic Nervous System:**

Sympathetic outflow to the resistance vessels is of utmost importance for the determination of the level of peripheral vascular resistance. In hypertension, the sympathetic outflow to the periphery is inappropriately high [5].

**Receptors:**

The contractile response to stimulation of post-junctional receptors by adrenergic agonists is increased in several vascular beds of hypertensive animals and in humans with essential hypertension.

In addition to nor-epinephrine, responses to other vasoconstrictors such as serotonin are also profoundly altered in hypertension. Indeed an increased vasoconstrictor response to secretion is the hall mark of most forms of hypertension but may also occur with aging.

In addition, the vasodilator responses to serotonin, which are mediated by the activation of the endothelium (Via 5-HT1 – serotonergic receptors) and the release of nitric oxide, may be altered in hypertension [6].

**Intercellular Signal Transduction Mechanism:**

For increase in vascular tone which is characteristic of established hypertension, intercellular calcium levels are crucial mediators. As a rule, in most forms of experimental hypertension, activation of Phospholipase-C pathway and formation of its products is more pronounced [9].

**Vascular Structural Changes:**

As demonstrated by Folkow, minimal peripheral vascular resistance is decreased in established experimental and human hypertension suggesting structural vascular changes at the resistance artery level in the disease process. More recent data strongly suggests that vascular remodeling, i.e rearrangement of the same number of cells with comparable cellular volume is much more important. These structural changes may be particularly important at later stages of the hypertensive process and contribute to the maintenance of increased peripheral vascular resistance[10,11].

**Renin-Angiotensin System:**

Since the first angiotensin-II receptor antagonists were introduced a few years ago, numerous clinical trials have been conducted on their use in patients with hypertension and their potential use in patients with congestive heart failure. The angiotensin-II receptor antagonists that have been labeled for use in hypertension by the U.S.Food and DrugAdministration (FDA) are losartan, valstran, irbestran, candesartan and telmistran. Other angiotensin-II receptor antagonists currently under investigation include eprosartan, tasosartan and zolarsartan. The renin angiotensin system is thought to play an important role in the development and/or maintenance of high blood pressure.Angiotensin-II is a potent vasoconstrictor hormone which also contributes to structural changes of the blood vessel wall through its proliferate and migratory properties in smooth muscle cells. Aldosterone has important renal effects i.e. sodium and water retention. The paradigm of a form of high blood pressure in which this system is primarily involved in reno vascular hypertension, particularly two-kidney-one- clip hypertension as well as ren-2 transgenic rats.Renin is an enzyme which transformsangiotensinogen to angiotensin-I which then is converted toangiotensin-II, the biologically active hormone. In addition to angiotensin converting enzymes, non-ACE peptidases are also able to transform angiotensin-I to angiotensin-II

At the receptor level angiotensin-II primarily activates AT1 receptors. In addition, AT2- receptors have been delineated although their functional role is uncertain. Indeed, all known vascular effects of angiotensin-II such as vasoconstriction, migration and proliferation have beenshown to be mediated through AT1 receptors. The renin angiotensin system is crucially involved in the development of hypertension. In addition to the circulating renin angiotensin system, the vascular wall renin angiotensin system has come much more into focus recently. Indeed, the conversion of angiotensin-I into angiotensin-II occurs in the blood vessels walls ACE is relocated in the endothelial cell membrane. The local vascular renin-angiotensin system is thought to play an important rolein the local regulation of vascular tone in hypertension and also inthe development of structural changes i.e. remodeling and hypertrophy occurring during the hypertensive process.

Furthermore, the more renin angiotensin system can interact with the sympathetic nervous system both centrallyas well as in peripheral neurons. The central effect of angiotensin-II could alsoexplain the increased sympathetic nerve activity in patients with renovascular hypertension.Two systems of nomenclature are usedin reference toangiotensin-II receptor antagonists: one system employs Roman numerals and the other is based on the amino acids that make up the A-I and A-II receptors (AT1 and AT2 receptors). Angiotensin-II receptor antagonists act by binding to specific membrane-bound receptors that displace A-II from its type 1 receptor subtype (AT1). These drugs therefore function as selective blockers. AT-II pressor effects are mediated by AT1 receptors. These receptors are widespread in organs and tissues but are found predominantly in vascular and myocardial tissue, the liver, the adrenal cortex (i.e. the zona glomerulosa tissue, which secretes aldosterone) and some areas of the brain.

The side effects of angiotensin-II receptor antagonists are comparable to those of placebo. Unlike ACE inhibitors, the angiotensin-II receptor antagonists are not significantly associated with cough. Prospective studies have shown that cough occurs in 7-15% or more patients treated with ACE inhibitors. The accumulation of bradykinnin and substance P, as well as the activity of Kinnase II, is thought to increase bronchial reactivity and the potential for development of the dry, persistent cough associated with ACE inhibitors. In addition, prostaglandins and leukotrienes may form from bradykinnin and contribute to bronchial inflammation.
Dizziness is a drug- related side effects that occurs in about 2-4% patients taking ACE inhibitors.
Clinically significant drug interactions have been reported with ACE inhibitors which undergoes extensive first-pass metabolism by cytochrome P450 enzymes. Drugs such as ketoconazole and troleandomycin inhibit cytochrome P450 and thus may reduce formation of the active metabolite of losartan. The clinical implications of potential interactions with angiotensin-II receptor blockers are still uncertain [9,10,11].

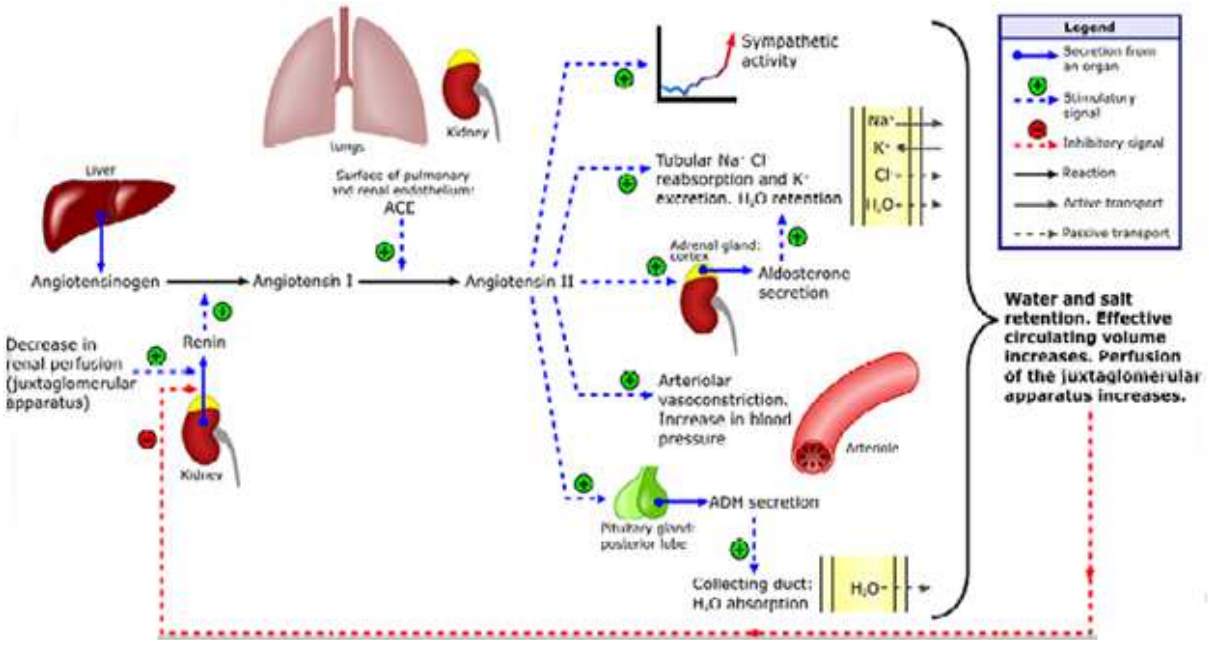


**Fig. No. Renin-angiotensin-aldosterone System.**

**Endothelial Control for Vascular Tone:**

More recently it has been recognized that the endothelium plays a crucial role in the regulation of local vasculartone by the release of relaxing and contracting factors. Nitric oxide formedfrom L-arginine via the activity of a constitutive form of Nitric oxide synthase, as well as prostacyclin which is formed from arachidonic acid by the enzyme cyclo-oxygenase are important relaxing factors. In hypertension, a number of derangements of endothelial cell function have been described which large part appear to be secondary to hypertensive process. In particular the basal formation of nitric oxide appears to be reduced, while receptor stimulated activation of the L-arginine nitric oxide pathway appears to be flaunted as well. Indeed, endothelium dependent relaxations or vasodilatation respectively, are reduced in experimental models of hypertension as well as in the forearm circulation and coronary circulation of most hypertensive patients [5,9].

**Role of Kidney in Blood Pressure Regulation:**

The kidney plays a particularly important role in the long term regulation of blood pressure. A key component in this context is the renal body fluid feedback due to pressure natriuresis mechanisms, which stabilize arterial blood pressure, as long as renal excretory capacity is not impaired. Thus a central hypothesis put forward by Guyton and co-workers suggests that essential hypertension may be a compensatory response for an inability of the kidney excretes the required amounts of sodium and water at a normal arterial pressure. A common feature of all renal disease causing hypertension is a decrease in the ratio of glomerular filtration rateto tubular absorption. This may come about due to primary reductionsin glomerular filtration rate (e.g. due to increased pre-glomerular resistance as it occurs in Goldblatt hypertension). Inspite of this extensive experimental work, the renal abnormalities responsible for essential hypertension remain elusive. This may due to the insidious onset of human hypertension as well as compensatory changes that many of the initial mechanisms within the kidney leading to hypertension [10,11,15].

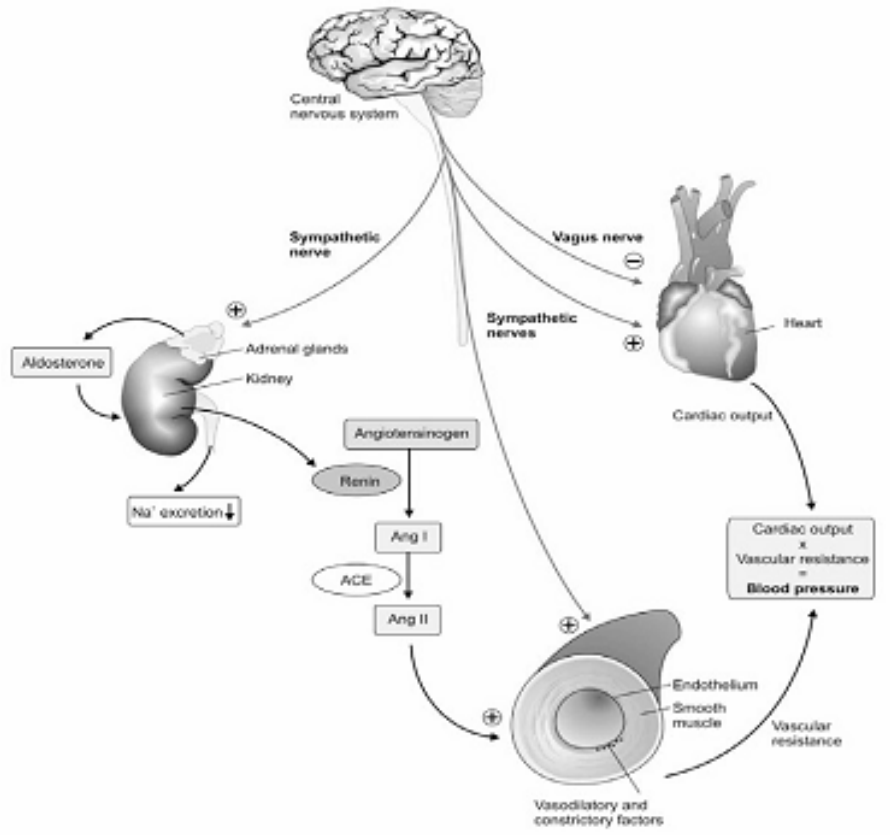


**Figure 1. A schematic diagram of the blood pressure regulation system**

**Management of Hypertension**

The object of treating systemic arterial hypertension is to reduce the risk of complications and to improve patient survival. This requires identification of any reversible risk factors, management of any associated clinical conditions, and treatment of elevated blood pressure itself. A combination of non pharmacological and

pharmacological therapy is required; the degree of intensity of treatment will depend on the severity of cardiovascular risk. In most instances, the discovery of hypertension commits the patient to a life time supervision and treatment. It is important to treat the whole patient and not just the blood pressure. Because of these considerations it is not particularly helpful to set up arbitrary levels of blood pressure at which treatment should be commended [1,3].

**A. Non-pharmacological management**

Several major life style risk factors contributes to hypertension and controlling of these factors are required for hypertension management [4,5].

a. Weight reduction
b. Low sodium intake
c. Avoidance of alcohol intake
d. Regular physical exercise
e. Healthy eating
f. Cessation of smoking
g. Others- These include stress management, micronutrient alterations and dietary supplementation with fish oil, potassium, calcium, magnesium and fibre. However, they have limited or unproven efficacy.

**B. Pharmacological management**

The following drugs are used to lower BP in Hypertension [5,7].

**I. Diuretics:**

**a) Thiazides and related drugs**

E.g. Hydrochlorothiazide, Chlorthalidone, Metolazone, Indapamide

**b) Loop diuretics**

E.g. :- Frusemide, Bumetanide.

**c) Potassium sparing diuretic**

E.g.:- Spironolactone, Triamterene, Amiloride

**II. Sympatholytic agents:**

**a) Centrally acting**

E.g.:- Clonidine, Methyldopa, Guanabenz, Guanfacine

**b) Adrenergic neurone blocking drugs**

i) Guanethedine, Guanadrel, Bethanidine, Debrisoquin.
ii) Ganglion blocking agents- Trimethaphan [other quaternary and tertiarylammonium compounds are no more used in the treatment of hypertension].
iii) Acting on nor epinephrine uptake mechanisms- Reserpine.
iv) Acting on Adrenergic receptors.

**c) Alpha- adreno-recceptor antagonists:** Prazosin, Terazosin, Indoramin.

**d) Combined alpha and beta- adreno-receptor blocking agent-** Labetolol

**e) Beta-adreno-receptors blocking agents:** Acebutolol, Atenolol, Metoprolol, Propranolol, Nadolol, Pindolol, Timolol.

**III. Vasodilators:**

**a) Arterial vasodilator**

E.g:- Hydralazine, Minoxidil, Diazoxide

**b) Venous vasodilators**

E.g:- Sodium- nitroprusside.

**c) Indirect vasodilators**

**i) Calcium channel blockers:**

E.g:- Nifedipine, Diltiazem, Verapamil, Felodipine, Amlodipine etc

**ii) Angiotensin converting enzyme inhibitors:**

E.g:- Gaptopril, Enalapril, Lisinopril, Ramipril, Perindopril etc.

**iii) Angiotensin II receptor antagonists**

E.g:- Losartan, Valsartan, Irbesartan, Candesartan, Telmisartan.

**Table : Effective combination in hypertension**

| Effective combination | Comments |
|---|---|
| b-blockers + diuretics | Benefits proven in the elderly, cost-effective. However, may increase risk of new onset diabetes |
| b-blockers + CCBs | Relatively cheap, appropriate for concurrent CHD |
| CCBs + ACEIs/ARBs | Appropriate for concurrent dyslipidaemias and diabetes mellitus |
| ACEIs + diuretics | Appropriate for concurrent heart failure, diabetes mellitus and stroke |
| ARBs + diuretics | Appropriate for concurrent heart failure and diabetes mellitus |

## Conclusion

Hypertension is a major risk factor for cardiovascular diseases, including heart failure, coronary heart disease, peripheral artery disease and stroke. Expenditure on the prevention or early identification and subsequent treatment of hypertension, both with and without medication, are thus well worthwhile ways to reduce the overall risk of cardiovascular morbidity and mortality.

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