BioCore Exploring Scientific Community

International Journal of Pharma Sciences and Scientific Research

Research Article ISSN 2471-6782

Risk factors, pathophysiology and management of hypertension

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Abstract

Hypertension, the major factor lead to mortality, is the increase in systolic and/or diastolic pressure and the risk factors which lead to hypertension are smoking, stress, salt, obesity etc. Different mechanisms contribute to the pathogenesis of hypertension including Cardiac output, Peripheral resistance, Renin–angiotensin-aldosterone system (Localized and centralized), Micro vascular alteration, Inflammation and Insulin sensitivity etc. which can be treated by using both pharmacological and non pharmacological approach. ACEIs, ARBs, CCBs and thiazide Diuretics are 1st line antihypertensive agents which are used mostly alone or in combination. ACEIs and ARBs are very effective for the patients with co–morbidities. Other agents like alpha adrenergic blockers are added to treat resistant hypertension. Methyldopa and and hydralazine are recommended for pregnancy and acute hypertension respectively. Where as lifestyle modification is a secondary way of controlling blood pressure. Keeping in view that hypertension cannot be cured rather it can be treated or the symptoms can be mask, patients should be properly counseled in order to prevent co morbidity, morbidity and mortality.

Keywords: Types of hypertension, Risk factor, Physical mechanism, Management, Treatment of Hypertension

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Citation: Tariq Javed et al. (2018), Risk factors, pathophysiology and management of hypertension. Int J Pharm Sci & Scient Res. 4:5, 49-61.

Received: June 22, 2018
Accepted: July 02, 2018
Published: August 08, 2018

Background

one of the most important risk factor which can lead to mortality is the hypertension, which means high blood pressure[1-2] which is also responsible for the cardiovascular and stroke like diseases[3]. It is the major health problem also known as silent killer because of its silent nature and hence quite difficult to identify the severity and the deaths due to this disease. It is necessary for the people to be aware of it[2, 4]. Hypertension can be controlled if diagnosed but it remains undiagnosed because in the early stages, it rarely shows symptoms. The controlling of the hypertension requires collaboration of government and civil society. Worldwide , about 17 million deaths per year occur due to cardiovascular diseases , out of which 9.4 million accounts for hypertension[2]. In 2013, statistical analysis was done by the American Heart Association, according to which in 2030, the prevalence rate of HTN will increase up to 7.2%. [5]. In 1990 – 1994 National Health Survey, the hypertension prevalence rate was 19.1% [6] and when the study was conducted on rural northern areas of the country , it came to know that the prevalence rate was 14% [7]. When the epidemiological study was conducted in rural areas of central Punjab, the results shown that with the passage of time, the prevalence rate of hypertension has increased in Pakistan [8].

What is hypertension?

Hypertension is defined as the rise in blood pressure, so the heart has to pump harder as the blood pressure increases. The blood pressure is usually expressed by two numbers which are written one above the other (systolic blood pressure and diastolic blood pressure).

Classification of HTN

In a healthy individual, the systolic blood pressure is 120 mmHg and the diastolic blood pressure is 80mmHg whereas when a person is suffered from the hypertension, the systolic blood pressure reaches to or above 140mmHg and diastolic blood pressure reaches to or above 90mmHg. When the blood pressure reaches above 115/75, then for each increase of 20mmHg in systolic blood pressure or 10mmHg of diastolic blood pressure, the chances of CV diseases get doubled.[9]

Stages of Hypertension			
CATEGORY	SYSTOLIC		DIASTOLIC
Normal	100- 120	And	60-80
Pre hypertension	120-140	Or	81 - 89
High blood pressure /HTN			
Stage 1 HTN	140-160	Or	90 - 110
Stage 2 HTN	>160	Or	>110[10]

Table1: stages of hypertension

Types of HTN

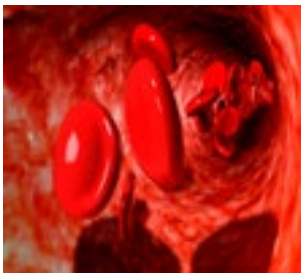
Primary hypertension

Primary hypertension also known as essential hypertension is the increase in blood pressure but due to an unknown cause which results in renal, cerebral and cardiac damages. It is associated with different risk factors like ageing, genetic(inappropriate increased function of RAS) and environmental factors(obesity, salt intake etc.), diabetes etc.[9, 11]. It is not a benign condition due to an end organ damage in children [12]. The ratio of cortical to cortisone in children having primary hypertension is high and there is no role of obesity in it [13]. Patients with the primary hypertension have low cognitive powers particularly memory and attention [14].

Excessive salt intake

genetic problems

stressful life

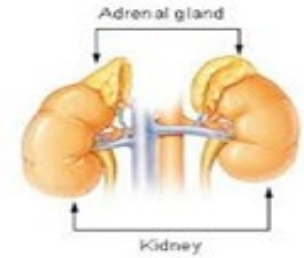


blood volume

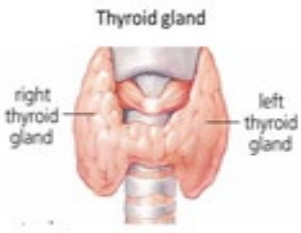
obesity[9, 11]

Secondary hypertension

It accounts for about 5% of the cases. The cause of this type of hypertension can be identified (if drug therapy given to patients is failed and BP is not controlled and it can be treated. The causes of this type of hypertension are renal dysfunction like renal artery stenosis, chronic renal disease, adrenal gland tumor etc.[9]



Kidney/adrenal problem



thyroid disorder


pregnancy


Sympathetic nervous sys.


Drugs

Risk factors

The various risk factors which can lead to hypertension are,

Smoking

It is one of the cause of hypertension and other cardiovascular diseases like myocardial infarction, stroke, and even sudden coronary death[15]. When a person gets exposed to tobacco smoke and active smoking, the number of segments of intracranial arteries increases with mixed atherosclerotic plaques[16]. Thus it is associated with the deterioration of health status[17]. On exposure to cigarette smoke ,there is a reduction in the nitric oxide which is a vasodilator and initiates vascular damaging thus leads to increased adhesion of platelets and macrophages which in turn enhance the inflammatory response. It also leads to tissue damage and its remodeling and thus structure of the vessel changes[18]. Passive smoking is greatly associated with the prevalence of hypertension [19].

Stress

The stress is associated with high blood pressure[20] . Due to an increase in stress level, the sympathetic nervous system activates and hence results in increased blood pressure[21]. By blocking the orexin receptor (present in the hypothalamic defense region), blood pressure can be reduced because on its blocking, cardiovascular system does not respond to stress.[22]

Salt

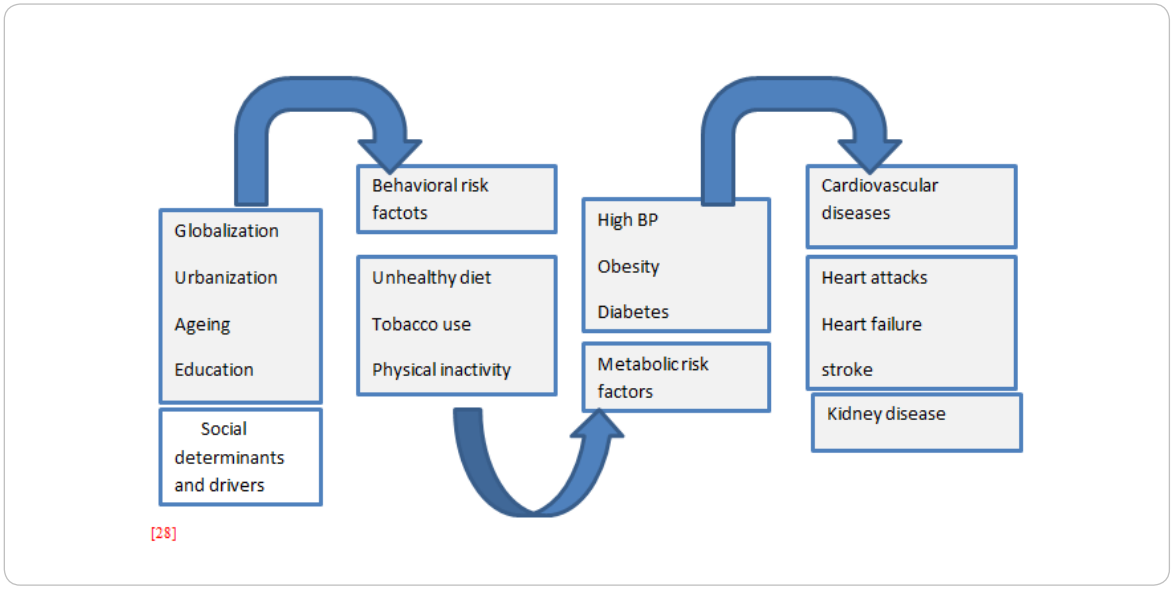
Salt intake leads to high blood pressure because of increased plasma volume and cardiac output, improper function of RAS and activation of sympathetic nervous system[23].

Obesity

The hypertension and diabetes which are more common in adults , are now also becoming popular in obese children than children bearing normal weight[24]. The most significant cause of hypertension is obesity in patients suffering from essential hypertension [25]. The factors which indicates the relation between the HTN and obesity are oxidative stress and inflammation, vascular injury, impaired autonomic nervous system[26].

Alcohol

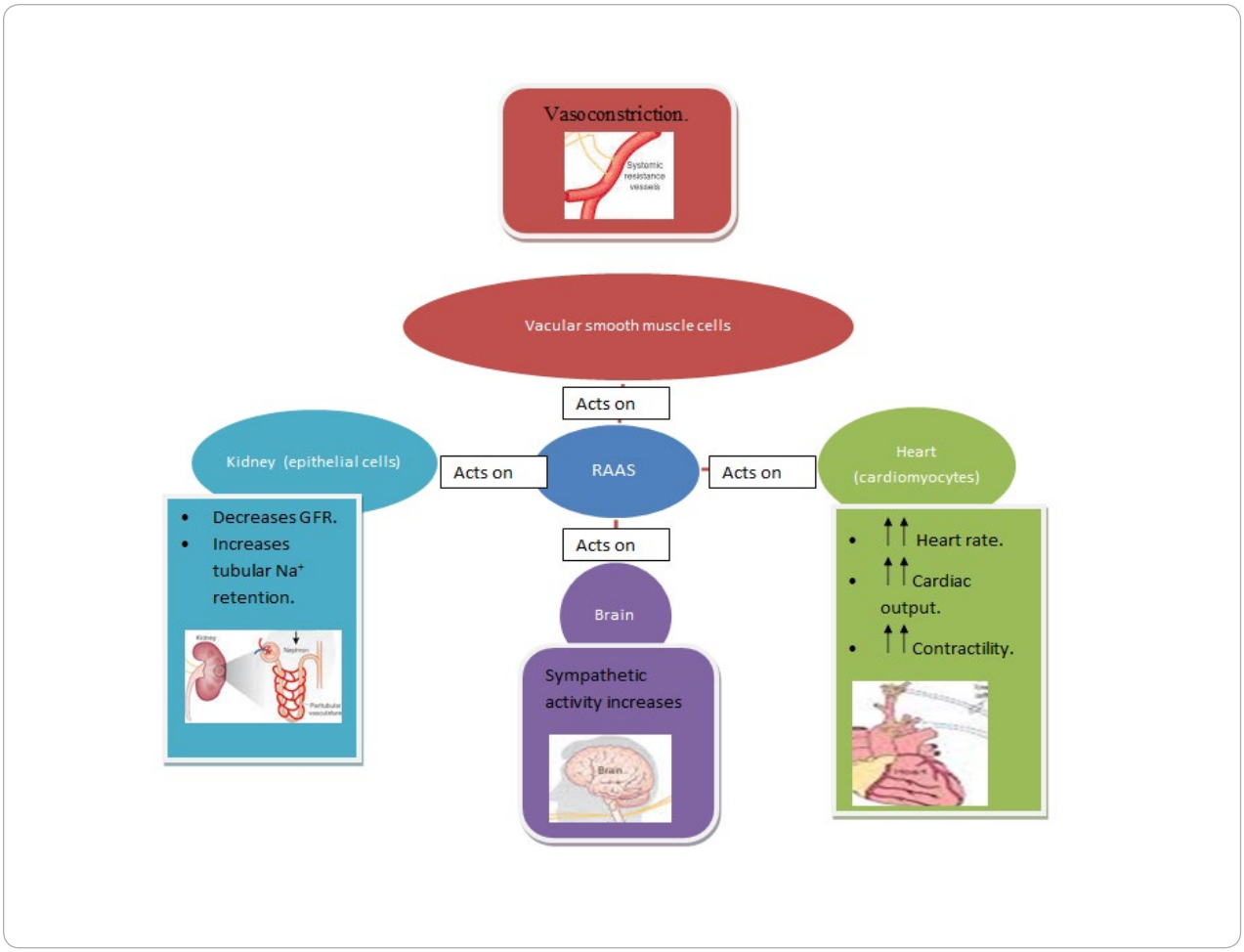
Excessive alcohol intake also leads to hypertension. Various mechanisms were proposed but still its mechanism is not clear. Several possible mechanisms are oxidative stress, vascular injury, less production of nitric oxide, impaired baroreceptors, stimulation of RAS system.[27]



[28]

Pathophysiology of Hypertension

Underline causes for the progression of hypertension in 95% cases are genetic or environmental whereas the rest of 5% are due to other diseases like stroke, cardiovascular disease or renal dysfunction[9] The common organ systems which are affected and involved in the development of hypertension are



Physical mechanisms which are involved in the advancement of Hypertension (HTN) are following[30]

1)Cardiac output and Peripheral resistance.
2)Renin-angiotensin-aldosterone system (Localized and centralized).
3)Micro vascular Alteration.
4)Inflammation.
5)Insulin sensitivity.

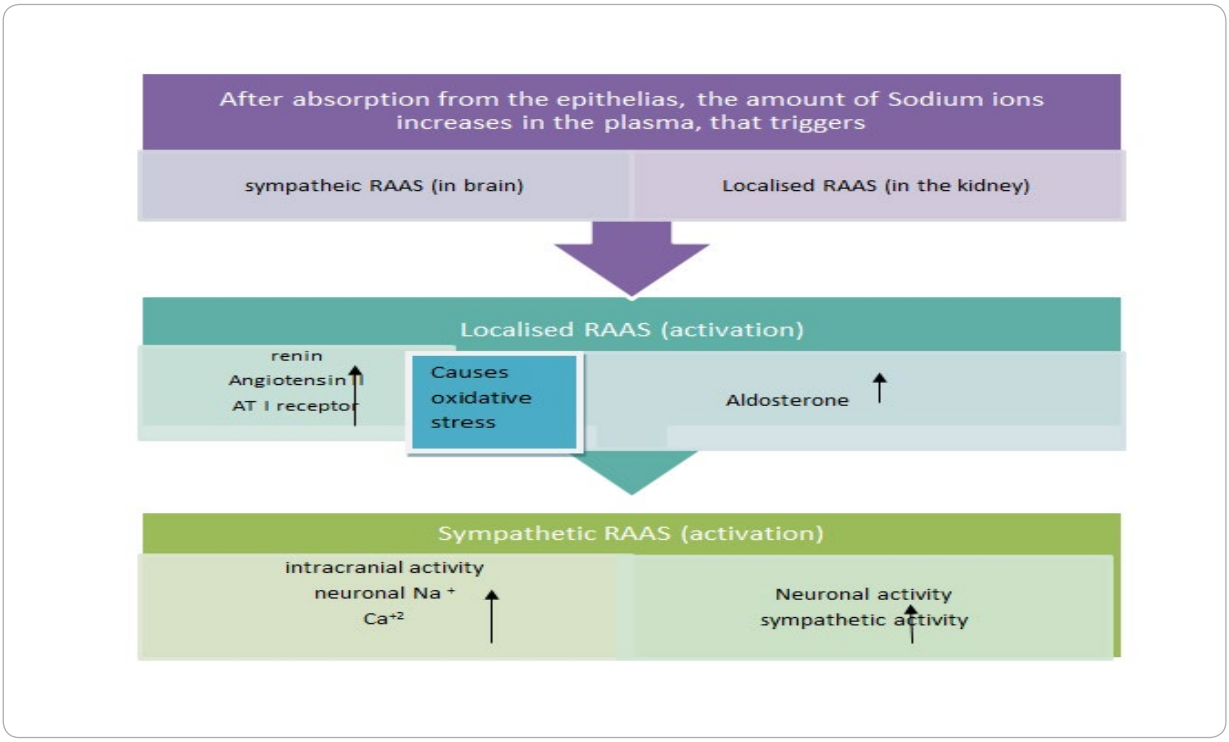
Cardiac output and peripheral resistance

The cardiac output and peripheral resistance, both are the important components to calculate blood pressure because they are essential to estimate systolic and diastolic pressures respectively. Increased peripheral resistance is one of the major contributors. this is due to the arteriolar constriction, which is most likely to be caused by cardiac dysfunction.[31-32] Many genetic and environmental factors also contributes in the elevation of cardiac output and peripheral resistance .Besides affecting the peripheral blood vessels, cardiac output has a major role in regulating Cerebral circulation, that also affects blood pressure [33] Cardiac output also increases in the obese patients due to increased amount of fats and plasma volume.[34]

Renin, Angiotensin and Aldosterone System (Localized and centralized)

Renin-Angiotensin and aldosterone system (RAAS) regulates the blood pressure by various mechanisms[35]. In addition to the maintenance, it also act as a marker for the onset of hypertension .[29] RAAS (Angiotensin-II) oriented hypertension is gender dependent, means it is more in the case of males.[36]

Brain being the control centre also regulates the circulatory system. Studies suggest that Brain-RAAS is more activated than peripheral RAS [37]. Being the major precursor of this system, Angiotensin II ,a neuropeptide plays a vital role in modulating blood pressure [38] and the RAAS receptors AT1a, AT1b are located in the cerebral part of the brain.[39] .One of the potential target is by reducing the nerve supplying the kidneys which can decrease the blood pressure.[40] Both the localized and centralized pathways by which RAAS can cause hypertension are depicted in the flow chart below:



Micro vascular Alteration

The reduced levels of nitric oxide or altered metabolic pathways are due to increased oxygen radicals that may lead to hypertension.[41] The bore of the arteriole is so small, that in these situations, if the vasculature is altered that means the perfusion of blood to the organs is reduced, due to inbuilt pressure, that can either result in ischemia or rupture of vessels which can lead to organ damage.[42] As the presence of reactive oxygen species can result in cell lyses and may lead to vascular modification.[36]

Role of inflammation

Tenacious inflammation results in vascular recasting that further transforms to hypertension[43] i-e due to the turn on and procreation of smooth muscle cells, endothelial cells and fibroblasts[44]. Inflammatory mediators cytokines , chemokines and PGE2 are involved in the signaling of hypertension as they increase the pressure of the blood by thickening the vessels.[45-46]

Insulin sensitivity

Due to altered nutrition and micro vascular relaxation, the insulin mediated metabolic functions are also disturbed, as a consequence of which insufficient supply of glucose to the tissues occurs and also leads to the reduce amount of endothelial nitric oxide [47-48], inflammation and oxidative stress ,mostly occurs in obese and diabetic patients. [47, 49]

Treatment

Usually patients of hypertension have co-morbidities so appropriate selection of antihypertensive agents is necessary.[50] In the United States 5 classes are primarily used to treat hypertension which is following

Class	%
angiotensin-converting enzyme inhibitors (ACEIs)	29
angiotensin receptor blockers (ARBs),	22
calcium-channel blockers(CCBs)	21
thiazide-like diuretics	24
beta-blockers	19[51]

Table 2

Angiotensin converting enzyme inhibitors

Both ACEIs and ARBs are generally recommended for primary hypertension.[52] ACEIs like Ramipril not only lowers blood pressure but also affect biochemical parameters. Significant reduction in the cholesterol, uric acid and fasting blood glucose level is noticed after the monotherapy with ACEIs (Ramipril).Thus this class of antihypertensive drugs is also the best option for the patient with the co-morbidities such as diabetes mellitus, hyperlipidemia and gout.[53] CV mortality and all cause mortality is limited in diabetic patients by ACEIs.[54]

Adverse effects

In comparison with ARBs they have somewhat more withdrawal rate due to adverse effects.[52] They have some side effects like hypotension, hyperkalemia and impaired renal function. Utilization of ACEIs can cause cough (in 5%-35% patients) and angioedema (up to 0.7% patients) which are their class adverse effects.[55]

Cough

Build up of bradykinin, prostanoids, substance P and more inflammatory neuropeptide in the upper respiratory tract and lungs produce this ACE inhibitor induced cough which can be treated by termination of therapy. Likelihood of this ACE inhibitor induced cough can be reduced with the co-administration of calcium channel blockers (Dilitiazim) and diuretics. Cough may move by persistent use of ACEIs.[56] [57-58] Smoking ,COPD and asthma raise the probability of ACE inhibitor induced cough and it is more in females.[59]

Angiotensin converting enzyme inhibitors (ACEIs)	**Angiotensin receptor blockers (ARBs)**	**Beta blockers**	**Calcium channel blockers (CCBs)**	**Diuretics**
Benazepril Captopril Enalapril Fosinopril Lisinopril Perindopril Quinapril Ramipril Trandolapril	Azilsartan Candesartan Eprosartan Losartan Olmesartan Valsartan Telmisartan	Labetalol Acebutalol Atenolol Bisoprolol Carvedilol Metoprolol Succinate Metoprolol Tartrate Nadolol Nebivolol Propranolol Acebutanol	**Nonhydropyridines** Dilitiazim Virapamil **Dihydropyridines** Amlodipine Felodipine Isradipine Nifedipine Nitrendipine	**Thiazide diuretics** Bendroflumethazide Chlorthalidone Hydrochlorothiazide **Loop diuretics** Bumetanide Furosemide Indapamide **Potassium-sparing diuretics** Amiloride Eplerenone Spironolactone Triamterene
Direct Renin inhibitors (DRI)	**Vasodilators**	**Central alpha agonists**	**Adrenergic depleters**	**Alpha adrenergic receptor blockers**
Aliskiren	Hydralazine Minoxidil	Clonidine Methyldopa	Reserpine	Prazosin Terazosin Doxazosin[9]

Table. 3: classification of antihypertensive agents

Angioedema

Mostly angioedema is noticed in females within 90 days of ACEIs utilization.[60] one of the rare form of angioedema is intestinal oedema which is presented by abdominal pain nausea and vomiting.[61]

Angiotensin receptor blockers

Clinically accessible ARBs are azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan that are having distinct pharmacokinetic profile.[62] ACEIs and ARBs reduce mortality in non dialysis dependent CKD patients.[63] ARBs also reduce CV mortality, all causes of mortality and the new onset DM where ACEIs cannot be used.[64]There are less chances of angioedema with ARBs when compared with ACEIs and direct Renin inhibitors(Aliskiren).[65]

Mechanism of action of ACEIs and ARBs

Renin angiotensin system regulates the blood pressure which involves Renin. Renin converts angiotensinogen to angiotensin by catalyzing this reaction. Then ACE causes the changing of Angiotensin I to Angiotensin II. This angiotensin II bind to AT1 receptor and then further biological actions proceeds. [66] ACEIs inhibit angiotensin converting enzyme and thus the conversion of angiotensin I to angiotensin II. [67] ARBs are the AT1 receptor antagonists which bind with different pockets of receptor due to slight variations in their chemical structure (But majority have biphenyl-tetrazol and imidazole groups).AT1 receptor is a G protein coupled receptor having 359 amino acids.[62, 68]

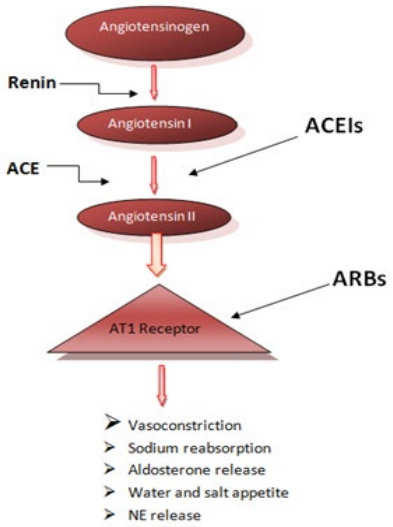


Figure 1

ARBs have some advantages like small extent of adverse effects and minimum first dose hypotension. These agents are suitable for elder patients with Diabetes mellitus and Heart failure.[69]

Direct Renin Inhibitors

Aliskiren is used orally which stops the conversion of angiotensinogen into angiotensin I. Aliskiren has similar activity as that of ACEIs ,ARBs and HCTH to control blood pressure in mild to moderate hypertension. [70-71]Combination therapy (Aliskiren and valsartan) is more effective than monotherapy to control blood pressure.[72]

Calcium channel blockers

Calcium channel blockers are divided into dihydopyridine and non-dihydropyridine.[73] For antihypertensive effect, CCBs antagonize L-type CaV1.2 calcium channels and decrease cells calcium flux thus dilate arteries and control blood pressure.[74-75] but some DHP also antagonize N–type calcium channels.[76]

Due to their efficacy and well acceptance, CCBs are also one of the most utilized antihypertensive agents both as monotherapy and combination therapy since 20 years.[77]But combination therapy is preferable then high dose monotherapy as it not only effectively controls systolic and diastolic blood pressure but also reduces the incidence of adverse events like rash and oedema.[78] As compared to the other combination therapies , combination of CCBs and ACEIs⁄ARBs reduce frequency of adverse events and cardiovascular events but have equivalent antihypertensive effect.[79] CCBs combination also have good renoprotective impact.[80] After alpha methyldopa ,Long acting nifedipine is suggested for hypertension in pregnant women.[81] Excessive utilization of calcium channel blockers may lead to edema, headache, flushing , tachycardia and constipation.[74]

Diuretics

Diuretics assist diuresis and primarily recommended antihypertensive agents as a second option .[82-83]They reduce blood pressure adequately and as compared to other diuretics Thiazide diuretics are mainly used .[84]

Thiazide diuretics

are highly utilized antihypertensive agents as a first line therapy. Thiazide diuretics reduce cardiovascular events and are more potent than beta blockers and ACEIs to diminish stroke.[85] They are classified into two types; Thiazide type (TT) diuretics and Thiazide like (TL) diuretics. TL diuretics are more effective to decrease cardiovascular events than TT diuretics So we can call TL diuretics as a drug of choice.[86] Hydrochlorothiazide is mainly used in United States from thiazide diuretics but now interest towards chlorthalidone use is rising [87] because Chlorthalidone can treat essential hypertension at low dose 6.25mg as a monotherapy but not Hydrochlorothiazide.[88] Hydrochlorothiazide is less effective than chlorthalidone ,indapamide, ACEIs, CCBs and beta blockers.[83, 89]

Loop diuretics

are not suggested because of less outcome data. They are not more effective than Thiazide diuretics but they have less side effects such as less hyponatremia, hypokalemia, and possibly less glucose intolerance.[90]

Aldosterone antagonists

They are suggested for resistant hypertension.[91] For example spironolactone is more potent than furosemide to treat resistant hypertension and also are harmless for kidney impairment patients.[92]

Side effects

Diuretics have some severe side effects such as volume depletion and electrolyte disorders. Thiazide and loop diuretics change electrolyte levels and can cause ventricular arrhythmias, coronary artery vasospasm or sudden death. [82] But with potassium-sparing diuretic combination, thiazide diuretics reduce the danger of sudden cardiac death. [83]

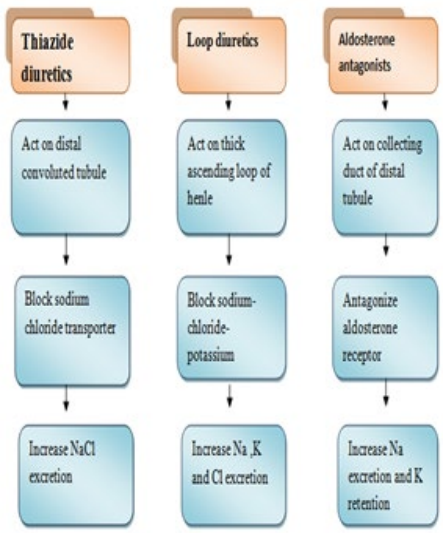


Figure 2: Mechanism of action

Beta blockers

Beta blockers are used since 45 years.[94]Now beta blockers are not suggested by some international treatment guidelines (JNC-8 and NICE UK) as a first line therapy.[95-96]But they are advised in younger hypertensive patients (<60 years) by The Canadian Hypertension Education Program. Because sympathetic activity is elevated by other antihypertensive agents in this age group.[94, 96]

Beta blockers are divided into first, second and third generation beta blockers. They can also be classified as vasodilators and non vasodilators. Vasodilating BBs (carvedilol and nebivolol) are more effective and well accepted than non vasodilating BBs (atenolol, metoprolol and propranolol). Because their utilization does not raise the likelihood of DM and weight gain. One of the vasodilating BBs Nebivolol not only effectively controls blood pressure by increasing levels of nitric oxide but also have fewer side effects. Due to various beneficial effects of Vasodilating BBs they should be considered by treatment guideline committees.[95-98].

Alpha adrenergic receptor blockers

To treat resistant hypertension, 2nd line antihypertensive agents like alpha adrenergic receptor blocker, vasodilators and centrally acting agents can be used as they do not show desired effect when used as monotherapy. They may be used in the case of allergic conditions with 1st line antihypertensive agents.[99] Combination of alpha blockers and beta blockers is efficacious.[100]

Central Alpha Agonists

Methyldopa is suggested as 1st line therapy to control blood pressure in hypertensive pregnant women.[101] Methyldopa has slight side effects like lack of energy and dizziness.[102]

Clonidine is not a first line antihypertensive drug but like spironolactone it also controls BP in resistant hypertension when added to triple regimen (ACEIs, ARBs and CCBs). [103-105]

Adrenergic Depleters

Reserpine is an alkaloid obtained from Rauwolfia serpentina. It is effective for hypertension when administered at low dose .[106] It has similar activity as that of the other 1st line antihypertensive agents to control systolic blood pressure but more clinical trials are required for the determination of dose.[107]

Vasodilators

Intravenous Hydralazine have efficacy for acute hypertension during pregnancy[108] it also control blood pressure in hospitalized children's but may produce hypotension.[109] Minoxidil is used for resistant and uncontrolled hypertension as reserve antihypertensive drug.[110]

Management of Hypertension

For the management of hypertension different guidelines have been established depending upon evidence base practice.

- JNC 8 guidelines.[111]
- ESH/ESC guidelines 2013[112]
- AHA/ACC guidelines 2013.[113]

Guidelines recommend the following instructions regarding the commencement of treatment in comorbid diseases.[114]

	JNC 7/8	2014 Guidelines (new)
Initiation of therapy required in co-morbid diseases.	>140/ 90 mmHg	>150/90 mmHg
age	Under 60	60 or above

Organizing the treatment protocol for the patients of hypertension involves both the use of pharmacological and non pharmacological means. It not only involves the diagnosis and prescription of appropriate regimen but also the proper counseling and adherence to the prescribed therapy.[115] The management should also involves the well-being, price and adverse effects that might be observed.[116]

Life style modification

Dietary modifications

Minimizing the consumption of salt, alcohol, oily foods and cigarette and switching to fresh vegetables prevents the raise in blood pressure.[9]

Potassium

Low intake of potassium has dangerous effect on blood pressure[117]. Adequate intake of potassium can reduces the chances of hypertension and is one of the best modification in the life style[118]. Potassium is required for electrolyte balance and body fluid volume maintenance, hence of great importance[119]. If the pregnant woman takes a diet which contains low potassium , there is a greater chance of morbidity in pregnant ladies suffering from preeclampsia[120].

Vitamin D

Vitamin D has role in lowering the systolic blood pressure but no role in lowering diastolic blood pressure. It is not an hypertensive agent [121]. Vit. D can be proved useful in treating the hypertension during pregnancy because it can prove many factors related to preeclampsia [122].

Weight loss

Weight reduction in patients' upto ≥10%. results in the lowering of fibrosis that helps in correcting the vascular remodeling and thickening of vessels.[123]

Exercise

Manual exertion reduces LDL-C, which can prevents atherosclerosis, a hall mark for cardiac diseases.[113]

Treatment goals in adult patients with comorbid diseases

The treatment is started with ACEIs, ARBs, CCBs or thiazide diuretics in Caucasian population, where as CCLBs or thiazide diuretics can be used as 1st line therapy.[111]

Treatment goals for geriatric patients

According to 2013 ESH/ESC1guidelines and the US guidelines for geriatrics, they recommend five classes of drugs for the treatment of hypertension in older patients' i-e ≥60 years of age. They are Calcium channel blockers, Angiotensin converting enzyme inhibitors, Angiotensin receptor blockers, Beta blockers and diuretics.[124] Whereas among them Beta blockers and CCBs are the drugs of choice. [125]

Abbreviations

HTN = Hypertension.

BP = Blood pressure.

CV = Cardiovascular.

DM = Diabetes mellitus.

CKD = Chronic kidney disease.

RAAS = Renin-Angiotensin-Aldosterone System.

ACEIs = Angiotensin converting enzyme inhibitors.

ARBs = Angiotensin receptor blockers.

CCBs = Calcium channel blockers.

BBs = Beta blockers.

DHP = Dihydropyridine.

HCTH = Hydrochlorothiazide.

NE = Nor epinephrine

LDL = Low density lipoprotein.

ESH/ESC = European Society of Hypertension and the European Society of Cardiology.

JNC = Joint National Committee.

AHA/ACC = American Health Association./ American College of Cardiology

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