A REVIEW ON HYPERTENSION AND ITS REMEDIES

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ABSTRACT
Hypertension is a major, worldwide health problem owing to its high prevalence and association with increased morbidity and mortality. Hypertension is a key risk factor for cardiovascular morbidity and mortality and is a leading cause of end-stage renal disease; approximately 7.1 million deaths per year can be directly attributed to poor control of blood pressure. Advances in the diagnosis and treatment of hypertension have had a major impact on management of this chronic disease. However, despite these advances, it is estimated that 1.56 billion people will suffer from hypertension by 2025. Further methods are therefore needed to reduce high blood pressure and its associated risks. The development of such treatments will be facilitated by an increased understanding of the pathogenic mechanisms underlying this condition. This review discusses the advances in our understanding of the mechanisms of hypertension and of the assessment, management and consequences of hypertension.

KEY WORDS: Hypertension, Cardiovascular diseases, Mechanism, Treatment.

INTRODUCTION
Hypertension or high blood pressure is a cardiac chronic medical condition in which the arterial blood pressure is increased. It is the most common cardiovascular disease and is a major public health issue in developed as well as developing countries. ¹,²
Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heartbeat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as pre-hypertension or hypertension. According to WHO (2003), Hypertension is a level of systolic blood pressure of 140mm Hg or above, or a level of diastolic blood pressure of 90 mm Hg or above, by repeated measurement over periods of several weeks.

Table 1: Classification of Blood Pressure in Adults

<table>
<thead>
<tr>
<th>Classification</th>
<th>Systolic pressure</th>
<th>Diastolic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>kPa</td>
</tr>
<tr>
<td>Normal</td>
<td>90–119</td>
<td>12–15.9</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>16.0–18.5</td>
</tr>
<tr>
<td>Stage 1</td>
<td>140–159</td>
<td>18.7–21.2</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥160</td>
<td>≥21.3</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>≥140</td>
<td>≥18.7</td>
</tr>
</tbody>
</table>

Symptoms Of Hypertension

Hypertension often has no symptoms. The only way to detect it is to check it regularly. However, now and then a person who has previously not been diagnosed with hypertension and may not have obesity as a factor may experience one of the known symptoms. These symptoms can vary greatly in intensity, and often people who don't have any elevation in blood pressure whatsoever can experience these same effects of hypertension.
1. Headache
2. Nosebleeds
3. Blurred vision
4. Palpitation
5. Dizziness
6. Tinnitus (ringing in ear)
These symptoms only indicate that it’s time to get the blood pressure checked.

**Causes Of Hypertension**

In recent years hypertension has become more and more common. There are several possible hypertension causes. The most common of them are:

1. Obesity
2. Alcohol intake
3. Cigarette smoking
4. High sodium intake
5. Anxiety
6. Diabetes
7. Endocrine disorders like adrenal disorders, thyroid disorders and Cushing syndrome.
8. Medications like appetite suppressants, corticosteroids, birth control pills, migraine medications.

**Different Types Of Hypertension**

1. **Primary Hypertension**
   Individuals typically suffer primary hypertension as a result of poor lifestyle habits. While this type of hypertension accounts for most of the cases diagnosed by doctors, the exact cause is unknown. However, some theories have suggested that in some people, a problem with the kidneys may cause the body to retain an increased amount of sodium, which, in turn, increases blood volume and pressure in the vessels. While medication may be required, dietary changes, stress management and physical activity are essential elements of treatment.

2. **Secondary Hypertension**
   Secondary hypertension is the symptom of an underlying medical condition such as kidney disease, problems with the liver, congestive heart failure, stress, sleep apnea or an endocrine disorder such as hyperthyroidism or Cushing's syndrome, which produce elevated levels of hormones. Renal artery stenosis is a frequent cause of secondary hypertension. Treatment of
secondary hypertension involves controlling the underlying medical condition or disease in addition to prescribing antihypertensive drugs.

3. Alcohol-induced Hypertension\textsuperscript{11}
Heavy drinking of alcohol may be one of the most common causes of secondary hypertension. Consuming too much caffeine can also cause a temporary increase in blood pressure. Caffeine stimulates the release of cortisol and adrenaline.

4. Isolated Systolic Hypertension\textsuperscript{12}
Isolated systolic hypertension occurs in people as they grow older. Build up of plaque in the arteries makes it more difficult for blood to flow through. Treating the elderly with diuretics not only decreases the risk of developing cardiovascular disease but may also reduce the risk of dementia and related depression.

5. Pregnancy Induced Hypertension\textsuperscript{13}
Some otherwise healthy women begin to suffer from hypertension after the twentieth week of pregnancy. In the majority of cases, these women are overweight or obese. The condition can be mild or rather severe. Other symptoms include retaining water and protein in the urine. The condition normally goes away within a few weeks following delivery. Pregnancy-induced hypertension may be due to preexisting hypertension, diabetes, kidney disease or carrying multiple fetuses. Women who are diagnosed with pregnancy-induced hypertension are at greater risk of preeclampsia during pregnancy. Symptoms may include headache, dizziness, swelling of the hands and face, nausea, vomiting and pain in the abdomen.

6. Medication Induced Hypertension\textsuperscript{14}
Certain prescription drugs and over-the-counter (OTC) medications can either cause or worsen hypertension. Non-steroidal anti-inflammatory drugs (NSAIDs), decongestants and weight loss supplements are common OTC drugs that can cause an increase in blood pressure. Corticosteroids, immunosuppressive and cancer drugs are among the prescription medications for which high blood pressure can be a side effect. These drugs constrict blood vessels and can cause kidney problems.

7. Malignant Hypertension\textsuperscript{15}
Malignant hypertension is considered to be a medical emergency as the blood pressure can suddenly rise to dangerous levels. A person can experience shortness of breath, chest pain, an
excruciating headache, seizures or even loss of consciousness as the blood pressure rises. Vomiting, blurred vision or blindness can occur as well. Because blood pressure quickly rises so high, a person is at risk for suffering stroke, heart attack, kidney damage or aneurysm causing bleeding in the brain.

8. **Preeclampsia**

Preeclampsia is a unique condition that is found in pregnant women. Other names can include toxemia, acute hypertensive disease and pregnancy-induced hypertension. Preeclampsia is common during a woman's first pregnancy but can also occur in future pregnancies as well. This is a very dangerous condition that can occur in 3 to 4 percent of all pregnancies and is the leading cause of fetal and maternal death, low birth weight, premature birth and still birth.

9. **Pre-hypertension**

Pre-hypertension is a condition that is in between normal blood pressure reading and high blood pressure reading and is usually symptom free. Pre-hypertension is defined as blood pressure readings between 120/80 and 139/89. People who have blood pressure reading in this range are also urged to make lifestyle changes such as losing weight, exercising, cutting down on salt, decreasing alcohol intake, eating more fruits, vegetables and more low fat dairy foods.

**Mechanism Of Hypertension**

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with total peripheral resistance (TPR) normal; over time cardiac output drops to normal levels but TPR is increased.

**Three theories have been proposed to explain this***

1. Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as Atrial Natriuretic Factor being secreted to promote salt excretion with the side effect of raising total peripheral resistance.
2. An overactive Renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume plus vasoconstriction leads to hypertension.
3. An overactive sympathetic nervous system, leading to increased stress responses.
It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Renin-Angiotensin System

The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a hormone system that regulates blood pressure and water (fluid) balance. When blood volume is low, juxtaglomerular cells in the kidneys secrete renin. Renin stimulates the production of angiotensin I, which is then converted to angiotensin II. Angiotensin II causes blood vessels to constrict, resulting in increased blood pressure. Angiotensin II also stimulates the secretion of the hormone aldosterone from the adrenal cortex. Aldosterone causes the tubules of the kidneys to increase the reabsorption of sodium and water into the blood. This increases the volume of fluid in the body, which also increases blood pressure.

If the renin-angiotensin-aldosterone system is too active, blood pressure will be too high. There are many drugs that interrupt different steps in this system to lower blood pressure. These drugs are one of the main ways to control high blood pressure (hypertension), heart failure, kidney failure, and harmful effects of diabetes.
Antihypertensive Drugs

Figure 2: Factors Affecting Arterial Pressure

History of treatment of Hypertension
Hypertension and its drug therapy have been remarkably improved in the last 50 years. Different classes of drugs have received prominence with passage of time in this period. Before 1950 hardly any effective and tolerated antihypertensive agent was available. Veratrum and sodium thiocyanate could lower BP but were toxic and difficult to use. The ganglionic blockers developed in 1950s were effective but inconvenient.
Reserpine was a breakthrough but produced mental depression.

Reserpine The therapeutic potential of hydralazine could not be tapped fully because of marked side effects when it was used alone.

Hydralazine

Guanethidine introduced in 1961, was an improvement in ganglionic blockers.

Guanethidine

The antihypertensives of the 1960-70s were methyldopa, β blockers and diuretics was consolidated in 1970s and selective α blocker Prazosin broke new grounds.
Prazosin

The antihypertensives of the 1980-1990s are angiotensin-II converting enzyme inhibitors (ACE) and calcium channel blockers. Angiotensin II antagonists are the latest antihypertensives.

Available agents\textsuperscript{26, 27}

1. DIURETICS

Diuretics help the kidneys eliminate excess salt and water from the body's tissues and blood.\textsuperscript{26}

1. Loop diuretics

\begin{center}
\textbf{Bumetanide (1)}
\end{center}

\begin{center}
\textbf{Ethacrynic acid (2)}
\end{center}

\begin{center}
\textbf{Furosemide (3)}
\end{center}
2. Thiazide diuretics

Torsemide (4)

Epitizide (5)

Hydrochlorothiazide (6)

Chlorothiazide (7)
3. Thiazide-like diuretics

Bendroflumethiazide (8)

Indapamide (9)

Metolazone (10)

Chlorthalidone (11)
4. Potassium-sparing diuretics

Amiloride (12)

Triamterene (13)

Spironolactone (14)

2. Adrenergic Receptor Antagonists

1. Beta blockers

Atenolol (15)
Metoprolol (16)

Nadolol (17)

Oxprenolol (18)

Pindolol (19)
2. Alpha blockers

Propranolol (20)

Timolol (21)

Doxazosin (22)

Phentolamine (23)
Indoramin (24)

Phenoxybenzamine (25)

Prazosin (26)

Terazosin (27)
3. Mixed Alpha + Beta blockers

Tolazoline (28)

Bucindolol (29)

Carvedilol (30)

Labetalol (31)
Despite lowering blood pressure, alpha blockers have significantly poorer endpoint outcomes than other antihypertensives, and are no longer recommended as a first-line choice in the treatment of hypertension.\textsuperscript{26}

3. ADRENERGIC RECEPTOR AGONISTS

Alpha-2 agonists

\begin{itemize}
  \item Clonidine (32)
  \item Methyldopa (33)
  \item Guanfacine (34)
\end{itemize}

4. Calcium Channel Blockers
Calcium channel blockers block the entry of calcium into muscle cells in artery walls.
1. Dihydropyridines

Amlodipine (35)

Felodipine (36)

Isradipine (37)

Lercanidipine (38)
Nicardipine (39)

Nifedipine (40)

Nimodipine (41)

Nitrendipine (42)
2. Non-dihydropyridines

![Diltiazem (43)](image1)

![Verapamil (44)](image2)

5. Ace Inhibitors

ACE inhibitors inhibit the activity of Angiotensin-converting enzyme (ACE), an enzyme responsible for the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor.²⁷

![Captopril (45)](image3)

![Enalapril (46)](image4)
Fosinopril (47)

Lisinopril (48)

Perindopril (48)

Quinapril (49)
6. ANGIOTENSIN II RECEPTOR ANTAGONISTS

Angiotensin II receptor antagonists work by antagonizing the activation of angiotensin receptors.
Candesartan (53)

Eprosartan (54)

Irbesartan (55)

Losartan (56)
7. Aldosterone Antagonists
Aldosterone receptor antagonists:
Spironolactone

8. VASODILATORS
Vasodilators act directly on the smooth muscle of arteries to relax their walls so blood can move more easily through them; they are only used in hypertensive emergencies or when other drugs have failed, and even so are rarely given alone. Sodium nitroprusside, a very potent, short-acting vasodilator, is most commonly used for the quick, temporary reduction of blood pressure in emergencies (such as malignant hypertension or aortic dissection). Hydralazine and its derivatives are also used in the treatment of severe hypertension, although they should be avoided in emergencies. They are no longer indicated as first-line therapy for high blood pressure due to side effects and safety concerns, but hydralazine remains a drug of choice in gestational hypertension.

\[
\text{Hydralazine (61)}
\]

9. Centrally Acting Adrenergic Drugs
Central alpha agonists lower blood pressure by stimulating alpha-receptors in the brain which open peripheral arteries easing blood flow. Clonidine
2. Guanabenz
3. Methyldopa
4. Moxonidine (62)
Some adrenergic neuron blockers are used for the most resistant forms of hypertension:

![Chemical structure of Reserpine](image1)

**Reserpine (63)**

![Chemical structure of Guanethidine](image2)

**Guanethidine (64)**

**Complications In Therapy Of Hypertension**

There are many different drugs available for treating hypertension, all of which may produce adverse effects. Unfortunately, the frequency of side effects makes it difficult for some patients to continue their long term use. While mono therapy is preferable, it is often necessary to use a second or even third drug to control blood pressure effectively, further increasing the likelihood that the patient will experience untoward reaction. This factor promotes the need to invent the better and safer drugs for long term use.

**CONCLUSION**

I hope that our brief review will help all those who are interested in developing potent antihypertensive drugs in the field of medicinal chemistry.

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