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Review Article

Resistant hypertension

Moke EG[1]*, Ekuerhare B[2], Enaohwo MT[3], Asiwe JN[4], Ofulue OO[5], Umukoro EK[6], Isibor NP[1]

[1]*Department of Pharmacology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State, Nigeria*
[2]*University Health Services, Delta State University, Abraka, Delta State, Nigeria*
[3]*Department of Human Anatomy and Cell Biology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State, Nigeria*
[4]*Department of Physiology, PAMO University of Medical Sciences, Port Harcourt, Nigeria*
[5]*Department of Physiology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State, Nigeria*
[6]*Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, Delta State University, Abraka, Delta State, Nigeria*

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*Address for Correspondence:

Emuesiri Goodies Moke, *Department of Pharmacology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Delta State, Nigeria.*

Abstract

Background: Resistant hypertension is a common medical challenge facing clinicians and specialists. Although, the prevalence is currently unknown but various clinical trials have suggested that this problem is not rare. Resistant hypertension is blood pressure that remains above goal despite the use of at least three antihypertensive agents including a diuretic. It is a subtype of hypertension that increases the risk of cardiovascular, cerebrovascular and kidney disease. However, it is important to distinguish between pseudo-resistant hypertension and apparent hypertension from true resistant hypertension as they are often misdiagnosed.

Objectives: This review focuses on resistant hypertension, its pathophysiology and established therapy.

Methodology: Relevant articles used for this review covered a period of 2008-2022 using search engines and databases including PubMed, Scopus, Web of Science, and Google Scholar.

Main observation: Evaluation of patients with true resistant hypertension includes appropriate blood pressure measurement, screening for causes of secondary hypertension and screening for interfering medications. Management of resistant hypertension that has proved successful includes non-pharmacological approach like lifestyle modification and optimization of pharmacological agents, often including the use of mineralocorticoid receptor antagonist.

Conclusion: Considering the future management of resistant hypertension, a bunch of new device-based therapies are under effective development. Of these, renal denervation and carotid baroreflex activation are two potential devices for the significant reduction of blood pressure. However, further study is necessary before these devices can be approved for the routine treatment of resistant hypertension.

Keywords: Aldosterone; Cardiovascular disease; Resistant Hypertension; Therapy.

1. Introduction

One of the most common chronic diseases in developing countries is hypertension[1]. There is a link between hypertension and the risk for cardiovascular disorders[1-3]. The pharmacological management of hypertension involves the use of first-line medications which includes diuretics, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta blockers and calcium channel blockers. Most hypertensive patients require a combination of antihypertensives to achieve their blood pressure target[4]. However, some patients develop a sub-optimal blood pressure response to a well-constructed anti-hypertensive therapy. This is known as resistant hypertension[5].

Resistant hypertension can be defined as the suboptimal response to a well-constructed antihypertensive treatment. According to recent guidelines, resistant hypertension can be defined as a blood pressure greater than 130/80 mmHg in a patient taking three or more antihypertensive drugs of different classes and a blood pressure less than 130/80 mmHg in a patient taking four or more antihypertensive medications[6]. Resistant hypertension is a common problem encountered by clinicians. It refers to a blood pressure that remains elevated despite the concurrent use of three (3) antihypertensive medications of different classes (one of them preferably a diuretic) at full doses[5,7].

Before resistant hypertension is diagnosed, pseudo-resistance hypertension should be ruled out. Pseudo-resistance hypertension could be due to error in blood pressure measurement, white coat effect and medication non-adherence[8,9]. White coat resistant hypertension might be responsible for about one-third of the classically defined resistant hypertensive patients[10]. Errors in blood pressure measurement can account for the misdiagnosis of resistant hypertension. Hence, the preparation of the patient, environmental conditions, size of the cuff and the techniques of blood pressure measurement can have a substantial influence on the blood pressure result. Studies have revealed that about 50% of the total resistant hypertensive patients are actually having pseudo-resistance hypertension and not resistant hypertension[11]. Thus, it is crucial to ensure accurate

blood pressure measurement before diagnosis of resistant hypertension[9].

Although, the prevalence of resistant hypertension is unknown but cross-sectional studies and hypertension outcome studies suggest that resistant hypertension is common[12,13]. In an analysis carried out by the National Health and Nutrition Examination Survey (NHANES), only 53% of the participants being treated for hypertension had their blood pressure controlled to less than 140/90 mmHg[14]. Also, in a cross-sectional analysis carried out by the Framingham heart study, only 48% of the treated participant had their blood pressure controlled to less than 140/90 mmHg and only 40% of the elderly participants attained a goal blood pressure[15]. In the data collected from the Framingham heart study, a higher baseline of systolic blood pressure was recorded along with older age and in the presence of obesity. The results from The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the Framingham study were similar where the older and obese participant had higher baseline systolic blood pressure and required more than two antihypertensives[16].

2. Methods

Relevant articles used for this review covered a period of 2008-2022 using search engines and databases including PubMed, Scopus, Web of Science, and Google Scholar. Keywords that guided the search included "resistant hypertension", "treatment", "pathophysiology", "comorbidities", and "cardiovascular". Articles unrelated from the subject matter were excluded.

3. Pathophysiology of Resistant Hypertension

Hypertension arises from the dysfunction of several mechanisms which help to maintain the blood pressure homeostasis. One of this dysfunction includes inappropriate renal activation of the sympathetic nervous system[17]. This leads to increased renin release from the juxtaglomerular apparatus which in turn causes renin-angiotensin-aldosterone system (RAAS) activation and sympathetic activity. This consequently causes vasoconstriction, inappropriate intravascular volume retention and increased cardiac contractility which then lead to high blood pressure.

The consumption of excess dietary sodium also plays an important role in the etiology of hypertension[18]. Also, most patients with resistant hypertension have been shown to have high levels of aldosterone as compared to those with normotensives[19,20]. This implies that excess aldosterone is key in aggravating hypertension. A study conducted recently showed that elevated aldosterone levels though, independent of renin levels corresponded to worsening hypertension across all stages of hypertension severity[21]. The findings from this study suggest that excess level of aldosterone contributes to the pathophysiology of hypertension. However, it should be noted that these factors can be further compounded by intrinsic kidney or renal factors[21].

However, in most cases, the pathogenesis of resistant hypertension is unknown but sometimes in few instances, it could be as a result of secondary hypertension. In the absence of secondary factors, the condition is mostly multifactorial. Some proposed mechanisms include genetic factors, abnormal sympathetic nervous system activation and dysfunction in the renin-angiotensin-aldosterone system. To a great extent, evidences have revealed the involvement of enhanced sympathetic nervous system activity as an underlying pathogenic mechanism of resistant hypertension[22,23].

4. The Role of the Renin-Angiotensin-Aldosterone System in Hypertension

The renin-angiotensin-aldosterone system (RAAS) is a hormone system saddled with the responsibility of regulating the blood pressure and maintaining electrolyte and fluid balance (Figure 1). It is comprises of three hormones which are renin, angiotensin and aldosterone, and is primarily regulated by the rate of renal blood flow[24,25].

When the blood pressure is low, the system acts by first of all releasing renin from the granular cells of the juxtaglomerular apparatus in response to any of these factors: sympathetic stimulation by beta-1 (β1) adrenoceptors, decreased perfusion pressure in the renal system and reduced amount of sodium reaching the distal convoluted tubule. Angiotensinogen is a precursor protein produced by the liver which is broken down by renin to form angiotensin I which is then converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II then binds to various receptors in the body and produces actions like vasoconstriction, increased sodium reabsorption, increased release of noradrenaline, vasopressin and aldosterone. Vasoconstriction causes an increase in the systemic vascular resistance and arterial pressure. Aldosterone and vasopressin also causes sodium and fluid retention respectively. Thus, increasing the blood pressure and volume. Hence, the renin-angiotensin-aldosterone system elevates the blood volume and pressure by increasing sodium and water reabsorption and the vascular tone. So, the RASS is activated when there is a fall in the blood pressure. A dysfunction in the mechanism of the renin-angiotensin-aldosterone system is thus said to play a role in the pathogenesis of resistant hypertension[26,27].

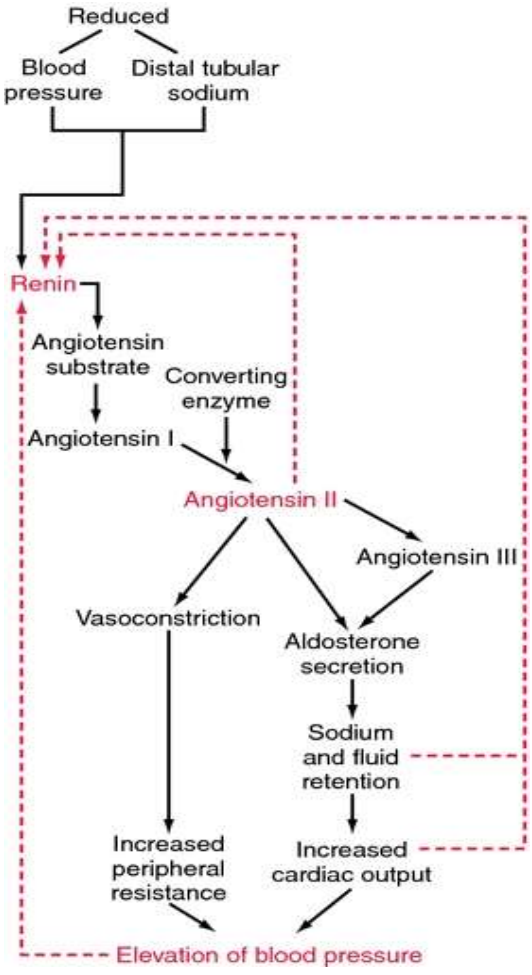

Figure 1: Role of the renin-angiotensin-aldosterone system in the elevation of the blood pressure

5. Resistant Hypertension Comorbidities

Multiple comorbidities have been linked with resistant hypertension. Some of these comorbidities include obesity, diabetes mellitus, albuminuria, ventricular hypertrophy, obstructive sleep apnea and chronic kidney disease[6].

Old age, obesity, presence of some co-morbid conditions like diabetes, cardiovascular disease, silent target damage such as left ventricular hypertrophy and chronic kidney disease were the main clinical characteristics that differentiated resistant hypertensive patients from those with controlled hypertension[23,28]. In a data obtained from the Spanish Ambulatory Blood Pressure Monitoring (ABPM) Registry, more than 8000 patients with true hypertension had a longer duration of hypertension, a history of previous cardiovascular event, target organ damage and diabetes[29].

Some several clinical conditions are frequently associated with resistant hypertension. These include conditions like hyperaldosteronism and obstructive sleep apnea. Hyperaldosteronism is common in patients with resistant hypertension and more than 20% of classical primary aldosteronism has been reported in resistant hypertension[30]. It has been revealed that excess aldosterone and constant intravascular volume expansion as shown by high levels of plasma natriuretic peptides frequently underlie resistant hypertension[7,31,32].

There is a link between visceral adiposity and aldosterone secretion. Hence, this supports the hypothesis that obesity contributes to excess aldosterone and thus, provides a possible explanation to the relationship between obesity and resistant hypertension[33,34]. Also, the correlation between excess aldosterone and obstructive sleep apnea syndrome has been shown. According to a research conducted, the prevalence of obstructive sleep apnea has been estimated to be more than two-thirds of patients with resistant hypertension[35]. Also, diabetes mellitus have been grately associated with resistant hypertension[36-38].

6. Causes of Resistant Hypertension

6.1. Drug-Related Causes

Some medications or pharmacological agents can interfere with blood pressure control. These agents can increase the blood pressure and contribute to the treatment resistance. However, the effect of these medications are highly individualized as some people experience severe blood pressure elevation while others manifest little or no effect. A common class of drug which worsens blood pressure control is the non-narcotic analgesics. These include non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen[39]. In particular, NSAIDs are linked with modest but predictable increase in blood pressure[40]. Also, other medications like sympathomimetic agents can worsen blood pressure control. Glucocorticoids can induce fluid and sodium retention which eventually leads to an increment in the blood pressure[41]. Erythropoietin agents have also been said to elevate the blood pressure in normotensive and hypertensive patients[42].

6.2. Secondary Causes

Patients with resistant hypertension usually have secondary causes of hypertension. However, the prevalence of this is unknown. Secondary causes of resistant hypertension includes obstructive sleep apnea, renal parenchymal disease, primary aldosteronism and renal artery stenosis[28,32,35]. Uncommon secondary causes include Cushing's disease, intracranial tumour, pheochromocytoma, hyperparathyroidism and aortic coarctation. Diabetes is also a secondary cause of resistant hypertension[36,37].

6.3. Lifestyle Factors

Some lifestyle factors like unhealthy eating, excessive sodium intake and drinking of alcohol can lead to resistant hypertension. Unhealthy eating can result in obesity. The mechanism of obesity-induced hypertension is complex but it is said to include increased sympathetic activity, impaired sodium excretion and the activation of the renin-angiotensin-aldosterone system[34]. Excessive sodium intake can contribute to the development of resistant hypertension and can counter the effect of anti-hypertensive agents[18].

7. Diagnosis of Resistant Hypertension

In the diagnosis of resistant hypertension, the medical history of the patient should be obtained and information like the duration, progression and severity of the hypertension should be documented. Also, the treatment adherence of the patient, response to the prior prescribed medications such as the adverse effects, current drug use including any over-the-counter medicines, supplements or herbal products, symptoms of possible secondary cause of hypertension should be recorded in the patient's file. The level of treatment adherence should be evaluated. In the clinical setting, only the patient's self-report can evaluate the level of treatment adherence[43]. Patients should be asked how successful they were in taking all their prescribed medications. Factors which can limit adherence such as adverse effects, drug cost and dosing inconvenience should be discussed with the patient. Family members of the patient may provide more specific assessments of patient's adherence to the prescribed medication. However, such input should be made in the presence of the patient.

Accurate blood pressure monitoring is essential in the diagnosis of resistant hypertension[44]. When measuring the blood pressure, it should be done in a conductive environment. The right size of the cuff should be used and proper care must be taken to ensure accurate measurement. An important tool in the diagnosis of resistant hypertension is ambulatory blood pressure monitoring (ABPM) [45]. It involves obtaining the blood pressure at fixed time intervals usually during a period of 24 hours away from the medical environment. ABPM can be used to identify pseudo-resistance hypertension particularly those with white coat hypertension.

Physical examinations are generally made to identify the secondary causes of hypertension. A fundoscopic examination should be carried out to evaluate the severity of retinopathy. Physical observations like the presence of carotid, abdominal or femoral bruits increases the chances of renal artery stenosis which is a secondary cause of hypertension.

Biochemical evaluation of resistant hypertension includes a routine metabolic profile (potassium, sodium, bicarbonate, chloride, glucose and creatinine), urinalysis and plasma renin activity used to screen for primary aldosteronism. The aldosterone/renin ratio is an effective test for screening primary aldosteronism[46]. The patient's dietary sodium and potassium intake can be evaluated via a 24-hour urine collection and the creatinine clearance can be measured.

8. Treatment of Resistant Hypertension

8.1. Non-pharmacological Treatment and Management of Resistant Hypertension

Non-pharmacological approach in the treatment and management of resistance hypertension includes: weight loss, dietary sodium reduction, cessation of alcohol ingestion, increased physical activity and eating healthily. Diet rich in fruits and vegetables, high in calcium, potassium and magnesium, high in low-fat dairy products and low in

saturated fats have been shown to cause a reduction in the systolic and diastolic blood pressure[47].

8.2. Pharmacological Treatment and Management of Resistant Hypertension

8.2.1. Withdrawal of interfering medications

Medications that interfere with blood pressure control should be withdrawn. Non-steroidal anti-inflammatory drugs (NSAIDS) have been said to interfere with blood pressure control[39]. NSAIDS block the two cyclooxygenase enzymes – COX-1 and COX-2. The inhibition of COX-2 enzyme can block its natriuretic effect which leads to increased sodium retention. NSAIDS also causes an inhibition of the vasodilating action of prostaglandins and leads to the production of vasoconstricting factors like endothelin-1[48]. Endothelins when over expressed contributes to high blood pressure via its potent vasoconstrictive property. These overall effects produced by NSAIDS can contribute to the induction of hypertension in a controlled hypertensive patient or a normotensive patient.

Sympathomimetic drugs like methamphetamine, pemoline, cocaine, ephedrine, MDMA and amphetamine can also interfere with blood pressure control[49]. These drugs mimic the adrenergic nervous system and raise the blood pressure particularly in patients with hypertension. These drugs causes the activation of adrenergic receptors which leads to vasoconstriction, increase in peripheral resistance and systemic arterial blood pressure.

Corticosteroid drugs particularly those with great mineralocorticoid effects produce the greatest amount of sodium and fluid retention[41]. Corticosteroid-induced fluid retention can be so bad and patients with already existing hypertension may develop treatment-resistant hypertension when these drugs are co-administered. The basic mechanism of action of corticosteroids in the worsening of blood pressure control is that they lead to overstimulation of the mineralocorticoid receptor, thus, leading to sodium retention. This in turn leads to volume expansion and a subsequent rise in the blood pressure.

The chronic use of oral contraceptives may interfere with blood pressure control despite pharmacological intervention[50]. Although, the mechanism responsible for the hypertensive effect of oral contraceptives is not clearly understood but the renin-angiotensin system may play a major role since estrogen stimulates the production of angiotensinogen in the liver. Immunosuppressants like cyclosporine and tacrolimus can worsen blood-pressure control by decreasing the excretion of water, potassium and sodium[51]. Erythropoietin has also been said to worsen blood pressure control. The possible mechanism of the hypertensinogenic effect of erythropoietin has been linked to the increase in cardiac output and system resistance[42]. It has also been associated with the impairment of acetylcholine mediated vasodilator response which leads to unopposed vasoconstriction.

8.2.2. Diuretic therapy

Findings from the evaluation of patients with resistant hypertension have revealed that treatment resistance was related due to a lack of or underuse of diuretic therapy[52]. Blood pressure control was improved by increasing the doses of diuretics or changing the class of the prescribed diuretic. Thiazide diuretics acts by inhibiting the sodium-chloride transported situated in the renal distal tubule. They act to produce natriuresis and diuresis. A decrease in sodium reabsorption leads to a decrease in the plasma volume and extracellular fluid. This in turn causes reduced cardiac output, increased rennin release and reduction in blood pressure. Considering the thiazide or thiazide-like diuretics, indapamide and chlortalidone have been shown to have greater blood pressure lowering effect than hydrochlorothalidone[53]. In the treatment of resistant hypertension in patients with advanced chronic kidney disease (CKD), loop diuretics are preferred agents[54]. Furosemide and bumetanide have a relatively short half-life. Hence, they should be dosed twice a day to avoid reactive sodium retention which is due to activation of the renin-angiotensin-aldosterone system and constant natriuresis.

8.2.3. The use of mineralocorticoid receptor antagonist (MRA)

Mineralocorticoid receptor antagonist acts to block the action of aldosterone on mineralocorticoid receptors[55]. It is a diuretic drug that competitively antagonizes the effect of aldosterone at the mineralocorticoid receptors. Aldosterone is known to be a mineralocorticoid that is synthesized by the adrenal glands and binds to the mineralocorticoid receptors situated in the cells of the renal tubules. When this happens, a complex is formed that favours the transcription of some DNA segments in the nucleus and leads to the formation of two transporters which are the Na+/K+ ATPase pump and a sodium channel known as ENaC. These transporters are known as protein transporters and they cause an increase in the reabsorption of sodium and excretion of potassium. Through the antagonist action of mineralocorticoid receptor antagonist, aldosterone is inhibited. Thus, resulting in an increase in sodium excretion, decreased body fluid and reduced blood pressure.

Examples of mineralocorticoid receptor antagonist include spironolactone, eplerenone, canrenone, finerenone and mexrenone. A common side effect of this class of drug is increased urination and significant hyperkalemia. Eplerenone may be more advisable for patients requiring spironolactone doses above 25 mg/kg because of its adverse effects such as breast tenderness and hyperkalemia. Eplerenone is a spironolactone analog with decreased adverse effects. In patients with renal dysfunction, it is necessary to adjust the dose of eplerenone because failure to excrete the drug via the kidney could lead to the accumulation of potassium in the body which is dangerous.

Mineralocorticoid receptor antagonists should be included when considering adding a 4th anti-hypertensive agent. When spironolactone was used as a fourth line agent for RH in a study from ASCOT, it resulted in a mean blood pressure decline of 20/10 mmHg[7].

8.2.4. Combination therapy

Numerous studies have shown that additive antihypertensive benefits can be attained by combining two or more agents of different classes[56,57]. This is true of thiazide-like diuretic which improves blood pressure control significantly when combined with most of all other classes of antihypertensives[57]. Perceptively, it seems most appropriate to combine classes of antihypertensives with different mechanism of action. A triple drug regimen should be standardized to include a drug that blocks the rennin-angiotensin system, particularly an ACE (angiotensin converting enzymes) inhibitor or ARB (angiotensin receptor blocker), a long-acting calcium channel blocker like amlodipine and a long-acting thiazide diuretic, preferably indapamide or chlorthalidone. ACE inhibitors and ARBs play a vital role in the management of resistant hypertension as it prevents the development of common comorbidities like chronic kidney disease and diabetes mellitus[7].

Some novel agents are presently being evaluated in the treatment of RH. For example, Endothelin. A receptor

antagonist exerts its actions by causing vasodilation. Hydralazine or monoxidil when administered at higher doses are also effective vasodilators. Vasopeptidase inhibitors reduce the production of Angiotensin II and prevent the destruction of natriuretic peptides. Also, aminopeptidase A inhibitor acts on the renin-angiotensin-aldosterone system at the level of the central control[21].

8.2.5. The use of device-based therapy

This allows for a long-lasting reduction in the blood pressure following a single intervention while bypassing the need for ongoing pharmacologic therapy. One of these device-based therapy is renal denervation (RDN). The renal nerves have efferent and afferent sympathetic innervation. The efferent fibers come from the sympathetic ganglion and are stimulated through the juxtaglomerular apparatus and are main regulators of the renin-angiotensin-aldosterone system. The sensory afferent fibers are responsible for the sympathetic outflow to the kidney and controls sympathetic efferent activity and cardiovascular hemodynamic. Numerous studies involving the use of animals have shown a drastic reduction in the BP after renal denervation. The selective disruption of the sympathetic renal nerves by radio frequency energy given by percutaneously inserted catheter through the femoral artery has been shown to significantly lower the blood pressure. A clinical report have revealed mean BP reductions around 30/15 mmHg at 12 months of renal denervation in patients and this has been found to be maintained in a small fraction of these patients followed-up for 2-3 years after the procedure[23].

Another device-based therapy is carotid baroreflex activation. This involves the stimulation of the carotid sinus nerves through implanted devices. This has been reported to achieve significant reductions of diastolic and systolic blood pressure.

9. Conclusion

Hypertension is a difficult clinical problem with a significant fraction of patients failing to attain blood pressure control despite pharmacological intervention. This is known as resistant hypertension. Such patients are likely to suffer end-organ damage eventually. However, some will achieve normal blood pressure with conscientious treatment plan. Patients must be approached in a step-wise manner starting with traditional antihypertensive agents followed by the addition of other agents to reach a quadruple or five-drug regimen if needed. In patients who still remains hypertensive despite pharmacological approach, there are promising interventional options which are still under development such as the device-based therapy.

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