Review article

High blood pressure and endothelial dysfunction: effects of high blood pressure medications on endothelial dysfunction and new treatments

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Hypertension is one of the most common chronic medical conditions and to this day has remained one of the important problems of public health. Because of relationship between endothelial dysfunction, atherosclerosis and high blood pressure, returning the endothelium-dependent vasodilatation is known as one of the important goals of treatment for high blood pressure. Drugs should be able to preserve endothelial function and reduce blood pressure. This has caused the most recent treatments and strategies to improve endothelial function. We review the mechanism of these drugs on endothelial function. Most of the drugs have a positive effect on improving endothelial function and the role of dihydropyridine calcium channel inhibitors such as nifedipine is obvious. Most studies showed lack of adequate control of blood pressure by monotherapy. A combination of calcium channel blockers and angiotensin converting enzyme has been proposed. The use of new drugs such as antioxidant, aldosterone antagonists and the pro-angiogenic factors with nonpharmacologic and pharmacologic therapy, can reduce blood pressure and has a significant impact on the function of epithelium.

KEYWORDS: Hypertension, Endothelial Dysfunction, Drug

BACKGROUND

Hypertension is one of the most common chronic medical conditions and affects about 72 million people in America. Only 68.9% of patient were aware of their problem, 58.4% of them were undergoing drug treatments and adequate blood pressure control was seen in only 50-30% of patients.[1-9] Hypertension has become one of the health problems due to high incidence of some factors such as obesity, dietary habits and machine lifestyle.[10-13] This problem causes a significant increase in risk of hypertension among young people and children.[14-15] Blood pressure (BP) hemodynamically is the force of the blood into the vessel wall, and increased blood pressure is caused by increased cardiac output or increased vascular resistance or both. Several studies have shown that at all levels of blood pressure, the risk of mortality in cardiovascular disease in proportion to the amount of high blood pressure can increase. Maybe the best and most practical definition of hypertension is level of blood pressure that the benefits of treatment exceed the risks of being untreated.[16-17] Accordingly, in adults, systolic blood pressure 140 mmHg or higher or diastolic blood pressure 90 mmHg or higher is defined as hypertension. The goal of diagnosis and treatment of high blood pressure is to reduce the risk of cardiovascular disease and deaths.[18,19] The most important characteristic of high blood pressure is being asymptomatic. Dizziness and blurred vision is seen in these patients rather than in healthy individuals. Most patients are completely asymptomatic before the complications of hypertension and this is the most important obstacle in the diagnosis and control of hypertension in the community. Symptoms may be caused by heart disease, stroke and kidney diseases or others which is an indication of the underlying cause for blood pressure like polyuria and excessive thirst due to secondary hyperaldosteronism in patients with hypokalemia, weight gain and muscle weakness in patients with Cushing's syndrome or symptoms of an attack of headache, palpitations and sweating in patients with pheochromocytoma.[20] Systolic blood pressure above 180 mmHg and diastolic blood pressure above 120 mmHg is named hypertensive crisis. Based on increased blood pressure, we can classify urgent and emergent hypertension. About one percent of patients with hypertension experience a hypertensive crisis in their life.[21] Hypertensive urgencies frequently present with headache (22%), epistaxis (17%) and muscle stimulation (10%). Hypertensive emergencies frequently present

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with chest pain (27%), dyspnea (22%) and neurological disorders (21%). Rapid increase in arterial blood pressure during hypertensive crisis can lead to severe abnormalities of organs such as acute aortic dissection, acute myocardial infarction, intracranial bleeding and kidney failure.[22,23] The mechanism of organ damage caused by high blood pressure is often changes in the capillary circulation. Changes in capillary blood flow are the main cause of hypertension and the first sign of hypertension and heart disease. As a consequence of elevated blood pressure, elasticity of the arteries is decreased and vessel wall damage occurs. In the affected areas, fat and cholesterol deposits eventually lead to block arteries. This mechanism is the basic of vascular damage that can be induced by high blood pressure.[17] Changes in capillary blood flow are the base of the organ damage that is caused by high blood pressure in brain, heart and kidney.[24] Cardiovascular disease can change vascular function and structure. In patients with hypertension, the interaction between different regulatory systems can damage the environment vessel wall. It was shown that the contraction of one the renal arteries in mice can cause hypertension.[25] This research indicated that hypertension leads to vascular damage. In other models, angiotensin II that as the most important biological factor in the renin angiotensin system is responsible for hypertension and vascular injury.[26] Recent research indicates endothelial dysfunction involves in this process. Cell proliferation, fibrosis and adhesion molecules in the vessel wall are features of endothelial dysfunction.[27] However, it was emphasized that the effects of immune cells and oxidative stress in renal vascular injury.[28] Our aim in this study was to review and summarize previous studies about drugs and new methods that are used in the treatment of hypertension. In this study, we want to show the relationship between endothelial dysfunction and high blood pressure and drugs that affect this process.

High blood pressure can be divided into two main classes, primary and secondary hypertension. Primary hypertension is when there is no specific medical reason to explain patient' condition. Approximately, 95-90% of hypertension cases are in this category. Secondary hypertension is indicated with high blood pressure that results from some conditions such as kidney and endocrine disease (adrenal adenoma or pheochromocytoma) and resistant hypertension which may lead to increased risk of stroke, heart attack, arterial aneurysm and chronic renal failure.[29] Drugs and substances that increase blood pressure (such as salt, alcohol and non-steroidal anti-inflammatory) and secondary hypertension causes resistant hypertension.[30] In this group of patients taking maximum tolerated doses of three antihypertensive drugs including diuretics, the blood pressure level does not reach the target level of treatment.[31]

Sustained hypertension

If blood pressure remained after using the maximum dose of at least two drugs for the specified time, the following factors should be examined:

1- Lack of interest in the patient to drug therapy or lifestyle changes.
2- Secondary hypertension (chronic kidney disease, sleep apnea).
3- Using drugs that increase blood pressure (non-steroidal anti-inflammatory and prednisolone).
4- Alcohol.
5- Too much salt intake (especially in patients that use angiotensin-converting enzyme inhibitors or angiotensin II receptor).
6- Interactions in measuring blood pressures.
7- Increase in the volume intake (especially in chronic kidney disease).[32]

In 2003, a new division for the prevention, detection, evaluation and treatment of blood pressure was published[33,34] and a new class called pre-hypertension was presented.[35]

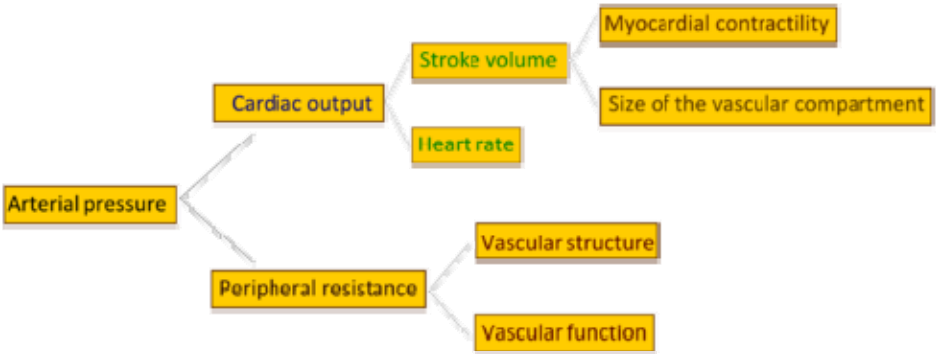

Figure 1. Role of cardiac output and peripheral resistance in pathophysiology of hypertension

1- Pathophysiology of hypertension

Pathophysiology of hypertension is caused by the interaction of several factors, including genetics, activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, endothelial dysfunction, impaired capillary blood flow and inflammatory mediators.[9]

1-1-Genetics:

Evidence of genetic influence on blood pressure has come from several sources.[36] In terms of blood pressure there are more similarities between people in a family rather than individuals from different families which represent a kind of inheritance.[37] Recently, genetic analysis has shown link between hypertension and various regions of the chromosomes.[35-42] Some studies detected reduction in gene expression, glutathione S-transferase Gstm1 in mice that suffered from high blood pressure.[43]

2-1- Autonomic nervous system:

The autonomic nervous system has central role in the stability of the cardiovascular system through controlling blood pressure, blood volume and chemoreceptor's signals. Autonomic system causes increase in cardiac output and vascular resistance and fluid retention. Disruption of this system, for example in hyperactivity in the sympathetic nervous system, increases blood pressure and involve in developing and sustaining high blood pressure.[44-48] Stress increases sympathetic output and continuous stress can cause vasoconstriction leading to increase peripheral vascular resistance that consequently increases blood pressure.[49]

3-1- Renin–angiotensin–aldosterone System:

Renin–angiotensin–aldosterone is another system that is involved in the extracellular fluid volume and peripheral vascular resistance, and if it is impaired, can lead to high blood pressure. Renin is an enzyme that plays a role in the contraction of arteries and maintaining the extracellular volume. So it involves in the regulation of blood pressure by hydrolyzing angiotensinogen to angiotensin I peptide. Angiotensinogen is secreted from the liver. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is a stronger vasoactive peptide.[50,51] Angiotensin II plays an important role in the pathophysiology of some diseases such as hypertension, atherosclerosis and heart failure, also in some mechanisms such as regulation of cell growth, inflammation and fibrosis. There are two important receptor of the angiotensin: AT1 and AT2. AT1 is responsible for most of the pathological activities of angiotensin such as cell proliferation, production of growth factors and cytokines, and fibrosis.[52] Moreover, angiotensin II has effects on the adrenal glands and causes aldosterone secretion. Aldosterone stimulates kidney epithelial cells which increase reabsorption of water and salt, thus increasing blood volume and blood pressure.[53] Recent studies have reported that obesity is a risk factor for high blood pressure because it causes activation of the renin–angiotensin–aldosterone system in fatty tissue.[54,55]

4-1- Endothelial dysfunction:

Endothelial cells are a barrier between blood and vascular smooth muscle cells. They have critical role in vascular function. Control of blood coagulation and fibrinolysis, the interactions between platelets and leukocytes with the vessel wall, regulation of vascular tone and role in the process of inflammation and vascular smooth muscle cell proliferation and death are activities of endothelial cells. Endothelial cells also secrete endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors (EDRFs) which have an opposite role in controlling vascular smooth muscle tone.[56-60]

2- Endothelial function

1-1- Endothelium-derived relaxing factors (EDRFs):

The endothelium secretes a number of vasodilator factors that nitric oxide (NO) is the most important one. NO is a free radical that is created from an essential amino acid, L-arginine, which in turn is converted to L-citrulline.[61] This process is catalyzed by endothelial nitric oxide syntheses. The pressure of the blood level into the unit of vessels will lead to increased ENOS activity.[62] A release of NO in vascular smooth muscle cells can activate guanylate cyclase (CGMP) which causes vasodilation.[63-73] Prostacyclin and endothelium-derived hyperpolarizing factors (EDHFs) are also important vasodilator factors that are involved in the dilatation of the arteries when increased vascular resistance occurs.[74] PGI2 is the most important prostaglandin secreted by the endothelium and its activity is vasodilatation, inhibition of platelet aggregation and inhibition of proliferation of vascular smooth muscle cells.[75] EDHF is a factor derived from the endothelium and one effect is especially in the dilated small blood vessels and its effect on diabetes can be reduced.[76] In physiological conditions, PGI2 and NO prevent platelet aggregation and adhesion of platelets and monocytes to endothelium and prevent the decrease in vessel lumen diameter.[77-79]

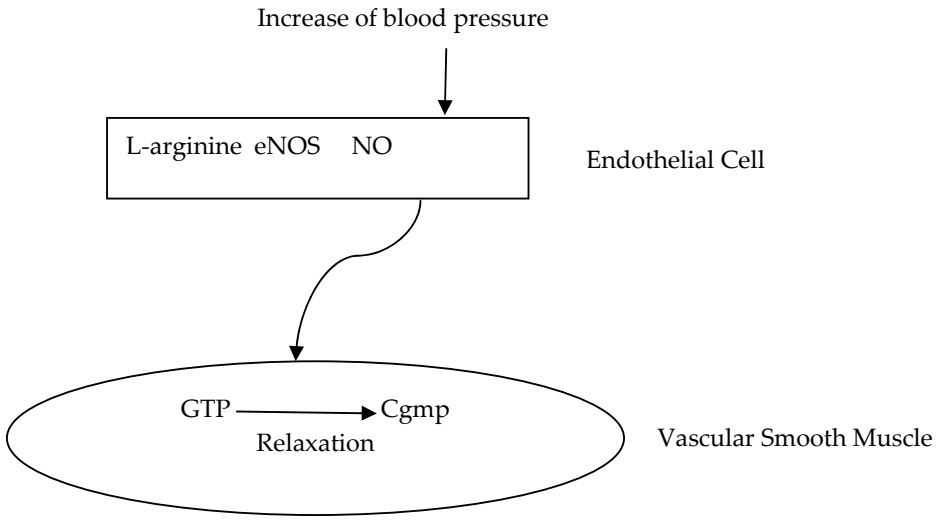

Figure 1. Production of nitric oxide (NO) by endothelial cells. NO is produced by the action of endothelial nitric oxide synthase (eNOS) on l-arginine. NO diffuses to vascular smooth muscle and causes relaxation by activating guanylate cyclase (GC), thereby increasing intracellular cyclic guanosine monophosphate (cGMP).

2-2- Endothelium-derived contracting factors (EDRFs):

Endothelial secretes several vascular contracting factors including: angiotensin II (ATII), endothelin I (ETI), dinucleotide uridine adenosine tetraphosphate (UP_4A), cyclooxygenase (COX)-derived prostanoids and reactive oxygen species (ROS).[80,81] To deal with the effects of EDRFs, these factors are produce higher than normal levels in hypertension and diabetes.[82]

Ang II:

Angiotensin I is metabolized to angiotensin II by ACE. Angiotensin II can activate angiotensin receptors and due to contraction by increased cytosolic calcium.[83-85] Increase in ACE activity leads to reduction of NO levels and increase in Ang II levels which result in vasoconstriction. Ang II is also involved in ROS production that alters dilated properties of NO.[86,87]

ETI:

Three isoforms of endothelin exist (ET-1, ET-2, ET3) that activate both ETA and ETB receptors. These receptors are present in vascular smooth muscle and coupled with Gq protein and produce IP3. IP3 increases calcium release from sarcoplasmic reticulum and leads to vasoconstriction.[88] Thromboxane A_2 and prostaglandin (derived from cyclooxygenase pathway) are also vasocontracting factors and act as antagonists of NO and prostacyclin. The cyclooxygenase pathway makes NO inactive by producing the superoxide anion and oxidative stress (OS).[89-96] The role of endothelial dysfunction in hypertension has been well established.[97] Hypertension is a pathophysiological condition that stimulates endothelial cells to produce contracting factors such as ECDF, thromboxane A_2, prostaglandin H_2 and oxygen free radicals that all of them act as NO's antagonists.[98] The oxygen free radical can breakdown NO molecules and applies theirs effects with this mechanism too.[99] Endothelial dysfunction was detected with impaired vasodilator factors and followed by changes in vessel wall structure. The most important changes due to endothelial dysfunction is reduction or absence of NO bioavailability especially to increase the OS that cause to breakdown of NO.[100] Despite much data about OS role in hypertension, the data obtained in human is less conclusive.[101] Evidences suggest that OS leads to overproduction of the ROS that have a key role in causing hypertension. Vasomotor system fluctuations cause ROS to act as a vasoconstrictor mediator stimulated by urotensin II, ET-1, Ang II. In pathophysiologic conditions, increased levels of ROS leads to vascular dysfunction and changes in oxidative damages.[102] ROS may directly alter vascular function or cause changes in the vessels tone by changing in NO bioavailability.[9] Evidences show that the super-oxide production in hypertension has a negative impact on production and performance of vascular endogenous NO, and endothelium-dependent vasodilation in vitro is dramatically reduced subsequent to increase blood pressure.[103-106] Also similar observations have been observed in humans suffering from high blood pressure.[107,108] Direct measurement of NO in endothelial cells and aortic arch in rats with hypertension showed decrease in NO release.[105,109] Therefore, the interaction between NO and

super-oxide is the most important factor in endothelium-dependent vascular dilatation defect in hypertension. In addition, recent studies have found evidence that impaired NO signal transmission pathways in animal models with hypertension have shown that production of guanylate cyclase enzyme and its activity in mice with hypertension intensity has decreased.[110,111] The role of super oxide in interference with the NO signal transmission is not well understood and more research is needed.[112] However, studies have shown that the role of endothelial dysfunction in high blood pressure is not only dependent on vasodilators or vasoconstrictors factors and other mechanisms such as platelet aggregation, proliferation and migration of vascular smooth muscle cells, monocytes and other adhesion molecules on endothelial function caused by other disorders, are also involved in this process[113-117] and the development process such as atherosclerosis and thrombosis.[118,123]

3- Drugs used to control blood pressure and their effects on endothelial function

Drug therapy can reduce blood pressure and mortality of cardiovascular disease.[124] In fact, for controlling blood pressure by pharmacological agents, reducing blood pressure below 90/140 mmHg is considered in all patients. In certain patients such as those with diabetes or chronic kidney disease, levels of blood pressure should be below 80/130 mmHg or 125/75 mmHg. This is very difficult to control blood pressure to this level and only 20% of patients in Europe and 50% of patients in America were treated with perfect controlling.[125-126]

Several drugs were used in hypertension and their pharmacokinetics and pharmacodynamics are different. The best treatment options are based on patient characteristics and pathophysiology of hypertension.[127] Choice of antihypertensive medications should be based on patient's age and clinical problems or organ damage. Because there are relationships between endothelial dysfunction, atherosclerosis and high blood pressure, we know returning the endothelium-dependent vasodilatation is one of the important goals of treatment for high blood pressure.[118] Drugs can be able to maintain endothelial function and reduce blood pressure. Since NO is the most important vasodilator which is secreted by endothelial drugs, these medications should improve changes in NO level.[128]

1-3- Interfering with fluid balance: Diuretics

These drugs inhibit transferring sodium and potassium chloride by affecting on the proximal tubules and distal tubules or both of them and inhibit resorption of these ions to plasma, thereby increase excretion of water and salt and reduce circulating volume. These drugs are used for treatment of heart failure, renal failure and nephrotic syndrome.[129] Chlorthalidone is the most effective diuretics. The most important limitation of using it is hypokalemia in some patients. Its side effects are resolved by amiloride (a potassium-holder diuretic).[130-136] Studies have shown thiazides do not have any role in reducing OS and improving endothelial function.[137]

2-3- Interfering with central nervous system:

1-2-3- β-blockers

β Blockers are the oldest class of cardiovascular drugs that are effective and safe in treatment of hypertension and cardiovascular disease such as coronary artery disease, myocardial infarction, heart failure, cardiac death and sudden death.[138-140] β-blockers interact with heart 1β receptors that are responsible for increasing cardiac output, often are used as an inhibitor of stimulation of sympathetic system secondary to the use of diuretics. The effects of this class of antihypertensive drug is through different mechanisms such as suppression of renin secretion by the glomerular cells of the kidney,[141] the inhibition of CNS sympathetic and reduced cardiac output by decreasing heart rate and contractility.[142] These drugs also reduce the risk of heart failure and mortality in patients.[139,140] A few studies were done on the effect of β-blockers on endothelium-dependent vasodilation. Schiffrin and Deng have shown that a treatment with atenolol does not lead to any improvement in response to acetylcholine, which is one of the mediators of vascular dilation.[143] Moreover, studies have shown that over a period of 3 months of treatment with these drugs, the response to acetylcholine and bradykinin and endothelium-dependent vasodilation in the brachial artery network in patients with hypertension, did not recover.[128] Third-generation drugs can have different effects. Experiments showed that nebivolol, a 1β receptor selectively antagonist, as a vasodilator, can cause the release of NO by stimulate the L-arginine-nitric oxide pathway.[144-148] In healthy humans, infusion of nebivolol into brachial artery network can increase the release of NO by stimulating L-arginin (L-NG-monomrthyl) (L-NMMA), which is an antagonist of endothelial vasodilator factors.[149] In addition, previous studies have shown that carvedilol is 1β receptor selective antagonist that is associated with 1α-blocker drugs can improve blood flow and vascular dilation in the brachial network and endothelial function.[150] This effect may be related to the antioxidant property of carvedilol.[151]

2-2-3- Calcium Channel Blockers (CCBs)

This category of drug inhibits transport of calcium into heart cells and vascular wall and thereby causing the blood vessels to be at rest. Decrease in intracellular Ca^{++} levels in vascular smooth muscle cells, leads to vasodilatation and decreased cardiac afterload. These drugs reduce coronary and peripheral vascular resistance and increase coronary blood flow and may be more effective in treating mild to moderate hypertension than β-blockers and diuretics.[152,153] Dihydropyridine types of calcium channel blockers such as nifedipine are more effective in preventing cardiovascular and cerebrovascular problems.[154,155] All data show that this class of drugs (especially dihydropyridine types) increases the endothelium-dependent vasodilatation in different vessels and in different animal models.[156-159] One year of therapy with nifedipine in patients with high blood pressure can reduce small artery resistance.[160] This effect of calcium channel blockers in coronary vascular bed and systemic circulation has been proven.[142,161] Studies have shown that 2 to 8 months of treatment with lacidipine increases vasodilation induced by acetylcholine and bradykinin function[162] but within 6 months of treatment with nifedipine it only increased the vasodilatory effect of acetylcholine.[163] Lacidipine also reduces plasma levels of the OS.[164]

3-3- Interfere with the renin-angiotensin-aldosterone:

1-3-3- ACE inhibitors

ACE inhibitors reduce mortality in patients with cardiovascular disease and heart failure.[165] Effectiveness and safety of these drugs in the long-term use make them an appropriate option for patients who have not sustained an examination.[166] Blood pressure has two curves: a fixed component that is dependent on cardiac output and vascular resistance or mean arterial pressure (MAP) and a pulse, but the pulse is related to arterial stiffness and wave reflection. Angiotensin II and its inhibitors are effective on vascular resistance and MAP while there is not enough information about the effects of these drugs on central or peripheral PP.[167] Note that angiotensin I acts through inhibition of NO-synthase or activation of the OS by activation of nicotinamide adenine dinucleotide glycohydrolase (NADH) and can cause endothelial dysfunction. The mechanism of these anti-hypertensive medications is to improve endothelial performance[168] and increase the plasma concentrations of bradykinin and vascular endothelial dilator factors.[113] Two years of treatment with cilazapril improved response to acetylcholine in subcutaneous capillary blood flow in patients with high blood pressure.[169,170] Similar results were observed in about three years of treatment with lisinopril.[171] In the absence of atherosclerosis in coronary arteries, perindoprilat improved vascular dilation[172] and this benefit of ACE inhibitors on endothelial function has well been observed in the renal circulation. In patient, ACE inhibitors improved systemic response to L-arginine and increased excretion of cGMP and caused vasodilation in this area.[173] At the end, treatment with enalapril can increase excretion of L-NMMA and stimulate release of NO in forearm circulation.[174,175] ACE inhibitors can also improve endothelial function in subcutaneous blood flow, arm network and pericardial.[176] These drugs also have anti-proliferative and anti-cell migration effects on smooth muscle and reduce the amount of OS. Other effects of these drugs can be pointed to the antiplatelet effect and increase endogenous fibrinolysis.[177] The use of these drugs had protective effects on renal and cardiovascular system, and this is why they are used as antihypertensive drugs like β-blockers and CCB.[178]

2-3-3- Angiotensin receptors inhibitors

Experimental data have shown that excretion of Ang II by releasing ET-I[179-181] producing of prostanoid PGH2 (a vasoconstrictor) by endothelium[182] and inhibition of NOS activity by activating protein kinase C,[183] has a negative effect on endothelial function. Increased synthesis of oxygen free radicals in the presence of Ang II have been shown to lead to defects in the function of acetylcholine.[182,143]

The most significant effect of this drug is vasodilatation via activation of NO and anti-cell proliferation property.[183-186] Studies have shown that a treatment with losartan in patients with high blood pressure, improves acetylcholine-dependent vasodilation,[187] while treatment with candesartan improves other aspects of endothelial function.[188]

4- Other drugs

The arterial dilators include hydralazine, fenoldopam, nicardipine, clevidipine and enalaprilat and nitroglycerin is a venous dilator.[189-194]

5- New treatments

1-5- Aldosterone antagonists

Aldosterone has devastating effects on the heart, vascular system and the kidneys and in patients with high blood pressure can cause organ damage. ACE inhibitors and Ang II inhibitors can only make relative decline in aldosterone levels, thus aldosterone can play a role in the pathophysiology of hypertension subsequent to increase of Ang II. Aldosterone binds to mineralocorticoid (MR) receptors that are involved in

sodium and water retention and potassium excretion[195] and when aldosterone secretion is excessive, abnormal activation of these receptors causes cardiovascular disorders, heart failure and hypertension.[196-198] Aldosterone also inhibits the secretion of NO[199] and many studies have focused on the benefits of blocking aldosterone to improve endothelial dysfunction. Spironolactone is an aldosterone nonspecific inhibitor that is commonly used in cardiovascular research. However, due to nonspecific aldosterone inhibitors' side effects, the use of eplerenone, a specific inhibitor of aldosterone that has more advantages than spironolactone, is recommended.[200]

2-5- Pro-angiogenesis factors

Angiogenesis means creating new vessels in the microvascular network and is the features of high blood pressure and disorder in capillary circulation and capillaries. Normal or high amount of NO increases angiogenesis levels.[201-203] Angiogenesis growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) stimulate the NO and also need to NO to apply their effect.[204,205] VEGF increases angiogenesis in ischemic heart disease and positive effects of gene therapy on VEGF has been well known.[206] Recently, it has been shown that placenta growth factor (PIGF) by increasing the amount of VEGF signals, increase the peripheral blood flow in animal models with myocardial infarction. Combination therapy with these factors and placental growth factor can enhance the effects of treatment.[207,209]

3-5- Antioxidant

Given the role of OS in the pathology of atherosclerosis and subsequent high blood pressure, antioxidants in recent years have been used to treat high blood pressure.[210] Antioxidant therapy improves endothelial function secondary to increase ROS levels and reduce blood pressure in animal models of hypertension.[211,212] Effects of hypertension on endothelial function may be improved whit antioxidant injection such as vitamin C into the systemic circulation.[213,214] Vitamin C and B are powerful antioxidants, which have resulted in improving endothelial function and provide diuresis.[215-217] In addition, increase in NO synthesis can increase coronary blood flow and reduce arteries resistance in the arm network.[218-223,144] Epidemiological studies have shown that high intake of vitamin B and C and beta-carotene reduces the risk of cardiovascular disease.[224,229] Due to the role of inflammation in the pathological process of atherosclerosis, vascular damage due to hypertension and thrombosis, new therapeutic interventions has been used to limit this process including the use of anti-inflammatory factors such as the cyclooxygenase inhibitors and anti-thrombosis factors.[230,231] In addition, interfere with the advance glycation end products (AGEs) pathway can be useful. AGEs increase contractility in left ventricle and stiffness in the artery wall and reduce the ability to be dilated. AGEs are formed with the production of free radicals that increase OS. A new drug product (AGEs-breaker ALT-711) with effect on AGEs reduced myocardial stiffness associated with age in dogs[232] and improved cardiovascular function in monkeys.[233]

CONCLUSIONS

Role of endothelial dysfunction in high blood pressure is well known that in addition to increasing the release of contracting factors including prostanoids, oxygen free radicals and endothelin, is reduced in bioavailability of nitric oxide. This is why high blood pressure medicines that can improve these disorders are particularly important. Converting enzyme inhibitors improve endothelial function in subcutaneous blood flow, renal and epicardial blood flow and increase the endothelial-dependent vasodilator and likely their effects are due to the EDHFs. Angiotensin type I receptor antagonists cause vasodilation in subcutaneous vessels but do not have any effect on capillary blood flow. These drugs also reduce the effects of endothelin. At present, most of the hypotheses indicate that the effect of calcium channel blockers can increase bioavailability of NO with their antioxidant effect and improve endothelial-dependent vasodilation in different vascular beds.[128] Pulse wave analysis showed that calcium channel dihydropyridine specific inhibitors and renin-angiotensin inhibitor reduce reflections of the pressure-wave on systolic central blood pressure and reduce arterial stiffness too. Due to the complementary role of these drugs, their combination improves clinical outcomes. The combination of calcium channel blockers and angiotensin converting enzyme inhibitors improve endothelial function and is more effective than other drugs alone. More recent studies show a decrease in central systolic blood pressure, pulse pressure and cardiovascular changes, with combination use of calcium channel blockers, angiotensin converting enzyme inhibitors and β-receptor inhibitors.[234] Although evidence indicates improved endothelial function using blood pressure medication, more clinical trials is necessary to prove whether improvement in endothelial function have a better prognosis for patients with high blood pressure or not? Furthermore, there is no evidence of the relationship between endothelial function and reduction in cardiovascular events.

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