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Overview of Hypertension Pathophysiology: New Insights into Oxidative Stress and Cytokines Roles

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Abstract

Hypertension is the most common health concern worldwide and one of the most major risk factors for cardiovascular disorders, stroke, myocardial infarction and renal disease, affecting up to 20-30 % of the general population. Also, hypertension is a complex and multifactorial illness with genetic, environmental, inflammatory and demographic factors. Increased oxidative stress and pro-inflammatory cytokines and reduced anti-inflammatory cytokines and antioxidant enzymes system characterize the hypertensive patients. Chronic inflammation induces endothelial dysfunction via elevated Ros generation through pro-inflammatory cytokines. Increased serum levels of pro-inflammatory cytokines such as leptin, IL-1 β , IL-6, IL-17, and TNF α have been associated with either decreased anti-inflammatory cytokine as IL-10 or IL-37 in hypertensive patients. Considering that inflammation plays a critical part in the progression of hypertension and its subsequent end-organ damage, hypertensive patients could benefit as a new therapeutic option from immunosuppressive therapies. This chapter aims to explore the role of several factors on the pathophysiology of hypertension, focusing mainly on oxidative stress and cytokines.

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Introduction

Hypertension is a serious public health problem along with its high prevalence worldwide [1]. However, the definitions were proposed by the Joint National Committee [2] and WHO are two popular definitions that are being used. According to WHO [3], hypertension was defined as Systolic Blood Pressure (SBP) equal to or above 140 mmHg and/ or diastolic blood pressure (DBP) equal to or above 90 mmHg. Joint National Committee7 (JNC7) defined normal BP as a SBP < 120 mmHg and DBP < 80mmHg. The grey area falling between SBP of 120-139 mmHg and DBP of 80-89 mmHg is defined as “prehypertension” [3]. While prehypertension is not in itself a medical condition, prehypertensive subjects are at higher risk for developing hypertension [4]. While most hypertension patients remain asymptomatic, some people with hypertension suffer headaches, lightheadedness, impaired vision, or diminished episode [5].

Globally, the number of patients with hypertension increased from 594 million in 1975 to 1.13 billion in 2015. In addition, the expected number of adults with hypertension will rise to 1.56 billion in 2025 [6]. The complication of hypertension is responsible for at least 45% of the deaths from cardiovascular disease

and 51% of the deaths from stroke [7]. Systemic low-grade inflammation can be defined as a 2- to 3-fold increase in plasma levels of cytokines and acute phase proteins [8]. Moreover, hypertensive patients have higher plasma concentrations of pro-inflammatory cytokines. Recently, Sproston and Ashworth [9] demonstrated that the higher plasma IL-6, IL-1, and TNF- α level in hypertensive patients as compared to normotensive patients [10]. This chapter aims to discuss the role of inflammatory mechanisms on the pathophysiology of hypertension.

Types of hypertension

Hypertension can be classified as primary (or essential) hypertension and secondary hypertension accounting for 95% and 5% of hypertensive patients, respectively [11].

Primary (essential) hypertension

Primary hypertension has no known etiology which can be clearly identified. Primary hypertension differs from secondary because elevation of the blood pressure occurs secondary to another known cause [12]. While primary hypertension is



unrecognizable cause, several studies have shown many risk factors for primary hypertension, such as age, family history, obesity, alcohol consumption and smoking [13]. Hypertension results from a dynamic gene- and environmental-factor relationship. Many familiar genetic variants have been identified, with small effects on blood pressure [14]. Several environments affects blood pressure; excessive consumption of salt raises blood pressure in individuals who are sensitive to salt; lack of exercise, obesity and depression [15] may play a role in particular circumstances. The possible role of other factors such as caffeine consumption and vitamin-D deficiency is less clear [16]. It is also thought that insulin resistance, common in obesity and a component of metabolic syndrome, correlates with hypertension [17].

Secondary hypertension

Many known cause results from secondary hypertension. This cause may be particular pathophysiology or disorder leading to hypertension or the creation of blood pressure may be due to the intake of certain foods or drugs [12]. Secondary causes of hypertension include renal parenchymal disease, Cushing 's syndrome, primary hyperaldosteronism, renovascular disease, aorta coarctation, pheochromocytoma, hyperthyroidism, and hyperparathyroidism. Alcohol- and oral contraceptive-induced hypertension and hypothyroidism are often included in this group [18]. Also, in adults and older patients, atherosclerotic renal artery stenosis, renal failure, and hypothyroidism are common causes [19]. Many causes of secondary hypertension include apnea during pregnancy and other prescription medication, herbal treatments and illicit drugs such as cocaine and methamphetamine [20].

Pathophysiology of hypertension

Although the etiology of essential hypertension is unknown, it usually begins in the fifth or sixth decade of life, is most often linked to increased salt intake and obesity, and has a close relationship to family history, underlining the possibility of genetic predisposition for the disease. The general symptom in the scenarios is the derangement of multiple mechanisms involved in regulating blood pressure and as such the mechanisms involved in the development of the disorder were the sympathetic nervous system, the renin angiotensin aldosterone system, the endothelial function plus sodium and water retention [21].

Both environmental and genetic factors play a key role in increasing Blood Pressure (BP) values. Hypertension is graded as a complex and multifactorial diseases after these factors are involved [22]. The majority of hypertensive patients have adaptable cardiovascular risk factors such as diabetes, overweight, smoking habits, sedentary lifestyle and salt ingestion. It is reconsidered to modify these factors to maintain a controlled blood pressure [23]. Obesity, insulin resistance, oxidative stress, compassion for exercise, endothelial dysfunction, increased inflammatory mediators, activated renin-angiotensin and obstructive sleep apnea have been proposed as potential causes for the development of hypertension [24].

Cardiac output and peripheral resistance

Maintaining normal blood pressure depends on the balance between the cardiac output and vascular peripheral resistance. Most patients with hypertension have normal heart performance but increased peripheral resistance [25]. In addition, large arteries or capillaries and small arterioles which contain smooth muscle cells decide the peripheral resistance. Contraction

of smooth muscle cells is thought to be associated with a rise in intracellular calcium concentration which may explain the vasodilatory effect of drugs blocking the calcium channels. Prolonged smooth muscle constriction is thought to cause structural changes with thickening of the arteriolar vessel walls potentially mediated by angiotensin, leading to an irreversible increase in peripheral resistance [21].

Autonomic nervous system

Sympathetic activation of the nervous system can cause both constriction of the arteries and dilation of the arteries. The autonomic nervous system, therefore, plays an important role in responding to stress and physical activity in maintaining normal blood pressure and mediating short-term changes in blood pressure [26]. A major player in the development of hypertension influencing blood pressure through two mechanisms, namely the efferent and afferent mechanisms, is the renal sympathetic nervous system. The efferent pathway carries signals from the nervous system to the kidney leading to (1) Increases renin release thereby activating the Renin-Angiotensin-Aldosterone System (RAAS), and (2) Increasing sodium and water retention, resulting in increased circulating volumes and (3) therefore, increased blood pressures [27].

Genetic factors

While separate genes and genetic factors have been linked to the development of critical hypertension, multiple genes are most likely contributing to a specific individual's development of the disorder. Even so, in subjects of one or two hypertensive parents, hypertension is around twice as severe, and several epidemiological studies indicate that hereditary factors account for around 30 percent of the variability in blood pressure in different populations. This figure can be derived from comparisons of parents with their monozygotic and dizygotic twin children, as well as their other children, and with adopted children [21].

Renin-angiotensin-system

Biochemical, physiological and behavioral studies have indicated that the Renin Angiotensin System (RAS) is primarily involved in producing hypertension via two tissue and circulating mechanisms [28]. The tissue RAS was in a state of excessively constant blood contact. Angiotensinogen, angiotensin AngI and AngII are developed locally and are also affected by the cells during which the AngII receptors are overexpressed [29]. Angiotensinogen production is a cause and effect of adipocyte hypertrophy and ends by the action of AngII in elevating force per unit area. In obese hypertensive, elevated rates and abnormally distributed free fatty acids were identified, during which they increased vascular α -adrenergic sensitivity and consequently increased α -adrenergic tone [30].

Mechanisms of obesity-induced hypertension

Indeed, epidemiological studies suggest that 65-75% of the risk for hypertension is attributed to excess weight [31]. The endocrinology of adipose tissue is a novel and most promising field of obesity and hypertension research which links these two pathological conditions. Adipose tissue is now a prolific organ that secretes many immunomodulators and bioactive molecules [32]. Based on the concept of infinite feedback gain, the arterial-pressure regulation system of diuresis and natriuresis tends to be moved towards higher levels of blood pressure in obese individuals [33]. Extracellular-fluid volume is expanded and the kidney-fluid apparatus is resettled to a hypertensive

level, consistent with a model of hypertension because of volume overload. Production of the plasma renin, angiotensinogen, angiotensin II and aldosterone shows substantial increases during obesity. Insulin resistance and inflammation can promote changed vascular function profile and hypertension as a consequence. Leptin and other neuropeptides are possible links between obesity and the development of hypertension [30].

Endothelial dysfunction

Endothelial dysfunction is one of the most possible inflammatory mechanisms which can promote hypertension [34]. The key underlying cause for endothelial hypertension dysfunction is the decline in Nitric Oxide (NO) supply as a consequence of elevated oxidative stress in these patients. Inhibition of the Nitric Oxide Synthase (eNOS) originating from endothelium is known as a possible etiological factor in blood pressure initiation. Moreover, eNOS is contributed to excessive vascular oxidative stress and vascular inflammation. Recently, the Endothelial Progenitor Cells (EPC's) have been implicated in the maintenance of arterial stiffness [25,35]. It is commonly manifested as vasodilatation dependent on endothelium due to an imbalance between vasoconstrictors and vasodilators [36]. Dinh et al. [8] mentioned that the inflammation can alter the rates of synthesis and degradation of vasoconstrictors and vasodilators including NO, and impaired NO bioactivity is associated with hypertension. For example, both CRP and TNF have been shown to attenuate NO development by destabilizing eNOS mRNA, which decreases the expression of NOS proteins and inhibiting TNF restore endothelial-dependent vasodilation in humans.

Inflammation in hypertension and metabolic syndrome

The inflammatory marker with the greatest correlation with hypertension is known to be the C-Reactive Protein (CRP). Through several clinical trials, it has been shown that hypertensive patients have generally raised levels of plasma CRP [37]. The higher baseline CRP levels are associated with a higher risk of developing overt hypertension [38]. The concept that systemic low-grade inflammation may precede hypertension.

Oxidative stress and hypertension

Antioxidant/oxidant balance is an important physiological regulator in the pathogenesis of hypertension. Endothelial dysfunction is a cause of hypertension partially mediated by oxidative stress, in addition antioxidants provide defense against vascular oxidative stress through neutralization of free radicals and protecting NO from inactivation [39]. The antioxidant administration enhances brachial artery flow-mediated dilation, decreases arterial stiffness, and alters markers of oxidative stress, including decreasing plasma lipid hydroperoxides [40]. Notably, Abdilla et al. [41] reported that humans with essential hypertension have reduced SOD activity, thus proved that individuals with hypertension exhibit increased oxidative stress. Hypertensive with other components of metabolic syndrome demonstrated elevated oxidative stress and exposed antioxidant capacities [42].

Reactive Oxygen Species (ROS) is a major cause of endothelial dysfunction, where decline in NO bioavailability via the direct chemical reaction of superoxide with NO, resulting in the formation of peroxynitrite and leads to final endothelial dysfunction [43]. Excessive ROS levels stimulate cellular damage by interacting with DNA, lipids, and protein resulting in further vascular impairment in either structure or function. Regarding other immune cells such as T cells, macrophages, and neutro-

phils express NADPH oxidase subunits and produce ROS; results in lower superoxide production and hypertension in response to Ang-II [44]

Clinically, the oxidative/antioxidant status was assessed by measuring oxidized/reduced glutathione, ROS-induced products of lipid peroxidation (malonaldehyde, MDA), genomic and mitochondrial DNA damage, plasma activity of SOD and Catalase (CAT) and activity of GSH-Px in hemolysed erythrocytes. These parameters were evaluated in hypertensive patients, some of them having criteria for Mets, and in normotensives [45]. The oxidative stress and the reduction in activity of antioxidant enzymes observed in hypertensive were not affected by the presence of additional components of the metabolic disorder [46].

Cytokines and hypertension

Hypertension is considered a chronic inflammation state [47]. The hypertensive patients are characterized by increase of pro-inflammatory cytokines secretion such as IL-1 β , IL-6, IL-8, IL-17, IL-23, leptin and TNF- α [10]. Inflammation stimulates endothelial dysfunction and atherosclerosis development through Reactive Oxygen Species (ROS) [48] which promotes pro-inflammatory cytokine production, increasing IL-6 expression resulting in decreasing Nitric Oxide (NO) production [47]. In hypertensive patients, TNF- α is remarkably increased and may play an important role in the pathogenesis and the development of hypertension. The increased angiotensin II in hypertension increase transcription and synthesis of pro-inflammatory cytokines such as TNF- α , which in turn activate the synthesis of angiotensinogen, whereby lead to the overexpression at downstream of angiotensin that finally contracts the vascular and facilitates hyperplasia [49].

Leptin with hypertension

Leptin was thought to be related to cardiovascular risk factors and increased as metabolic disorders increased risk [50]. Some studies have shown that the concentration of serum leptin increases with the increasing levels of body fat especially subcutaneous fat [51]. Also, several studies found that leptin levels increased with an increase in the number of metabolic disorders [52]. Besides this, Patel et al. observed that leptin can be a significant link in the pathogenesis of hypertension and heart disease caused by obesity and metabolic disorder [53].

It is now well accepted that leptin can trigger the sympathetic nervous system through both local peripheral actions and centrally mediated hypothalamus effects [54]. However, acute systemic administration of leptin was associated with peripheral activation without elevation of the sympathetic nervous system in MAP [55]. The lack of impact of leptin on arterial blood pressure in normal subjects may therefore reflect a balanced action of vasodilatation primarily mediated by NO and vasoconstriction primarily mediated by the sympathetic nervous system, resulting in a neutral hemodynamic action. [56].

Interleukin (IL-1 β) with hypertension

Resistant hypertension individuals have higher levels of inflammatory cytokines (Such as IL-1 β) as well as increased arterial stiffness and detectable IL-1 β levels are associated with arterial stiffness which means that inflammation plays a possible role in the pathophysiology of resistant hypertension [57]. The positive correlation found between IL-1 β and the blood pressure may be due to IL-1 β directly triggered contractile responses and enhanced those to the α 1-adrenoceptor agonist,

phenylephrine [58]. Together with the IL-1 β -mediated impairment of endothelium-dependent vasodilatation, such increases in contractile activity could conceivably contribute to increased total peripheral vascular resistance, which is a major determinant of blood pressure [59] and levels of IL-1Ra were found to be elevated in patients with essential hypertension compared with normotensive individuals [60], and this might be indicative of a compensatory response to offset elevated concentrations of IL-1 β [59].

Interleukin (IL-6) with hypertension

Several cytokines (e.g., TNF α , [interferon gamma], IL-1 β , and IL-6) are expected to cause acute and chronic inflammatory thrombo-inflammatory responses, with IL-6 being considered a cardiovascular disease clinical biomarker [61]. IL-6, IL-6R, and T-cell-dependent IL-6 signaling in Ang II-induced thrombo-inflammation, which may provide new therapeutic possibilities for drug discovery programs for the management of hypertension [62]. Moreover, Chamarthi et al [63] revealed the relation between hypertension and inflammation and provided human data supporting previous animal studies evidence that IL-6 plays a role in hypertension mediated by ANGII. Particularly, compared with rates in a liberal sodium diet, neither IL-6 nor CRP were higher with a low salt diet triggering the RAS, suggesting that a low sodium diet is not inflammatory despite increased RAS activity

Interferon gamma with hypertension

An essential mechanism by which IFN- γ may promote hypertension is its ability to induce angiotensinogen expression in both hepatocytes and the proximal tubular cells of the renal [64]. While angiotensinogen is not considered a rate limit for the systemic production of angiotensin II, its role in angiotensin II tubular development appears more important [65]. This angiotensin II promotes reabsorption of sodium and volume in both proximal and distal nephron. This is mediated by actions on the apical sodium hydrogen exchanger 3, basolateral Na / HCO₃ co-transport, and Na-K ATPase in the proximal tubule. Thus, it is conceivable that infiltration of T cells releasing IFN- γ could modulate local angiotensinogen production, increase sodium reabsorption and worsen hypertension in a feed-forward fashion [64].

Interleukin 17 with hypertension

Many studies have established a subset of T cells in cardiovascular disease that are distinguished by the development of IL-17 (Th17 cells) [66]. Recent evidence also supports IL-17 's function in cardiovascular illness and hypertension [67]. In turn, IL-17 induces IL-1, IL-6, and TNF- secretion, also associated with atherosclerosis and hypertension [68]. In order to assist these results, IL-17A inhibition regulated the penetration of inflammatory aortic walls into mice. Synthesis of IL-17 in the aortic media is also induced by infusion of Ang II in mice and humans [69]. Although IL-17A is associated with Ang II hypertension, renal dysfunction and renal sodium transporter modulators, studies indicate that IL-17A or IL-17RA receptor subunit antibodies could be a novel adjunct hypertension therapy [10].

IL-10 with hypertension

IL-10 is a multifunctional and active anti-inflammatory cytokine. IL-10's primary function is to restrict and remove inflammatory responses by inhibiting a wide range of immune parameters [70]. It was shown that IL-10 improves endotheli-

um-dependent relaxation by inhibiting NADPH oxidase activity in Ang II-hypertensive rats, improving their blood pressure [71]. However, the direct interplay between IL-10 and VSMC contractility during hypertension remains an unexplored area. Lima et al [72] Show a strong IL-10 effect on smooth, moist muscle cells. We showed that the absence of endogenous IL-10 when infused with Ang II resulted in increased vascular constriction; whereas exogenous IL-10 infusion prevented this effect, suggesting that IL-10 is capable of controlling vascular smooth muscle contraction and partially preventing Ang II actions.

IL-37 with hypertension

IL-37 has important anti-inflammatory, immune deviator, immunosuppressive, anticancer and metabo-regulatory effects. IL-37 dramatically reduces the release of cytokines in macrophages and dendritic cells (DCs). The IL-37 binding to its receptor activates Signal Transducers and Activators of Transcription 3 (STAT-3) and inhibits nuclear factor-kB (NF-kB) signals [73]. In addition, IL-37 has an important role in keeping plaque stability in fibrous caps in atherosclerosis and reduces the inflammation associated with atherosclerosis [74]. The protective role of IL-37 in hypertension has not been clearly investigated. Therefore, further studies are needed to fully investigate the therapeutic potential of IL-37 [75]. Furthermore, genetic variants in inflammatory cytokine genes may have the ability to alter the regulation of transcript synthesis or function and a change in the role or the quantity of a specific cytokine which may lead to the initiation or inhibition of the inflammatory process (Yan *et al.*, 2015) [76] and immune-mediated therapies targeting cytokines or resident adipose tissue macrophages in obese individuals could be useful as therapeutic options [77].

Conclusion

The available evidence reinforces the claim that both oxidative and cytokine stress could play a vital role in the hypertension pathway. Salt intake, obesity and insulin resistance, the renin-angiotensin system, and the sympathetic nervous system are among the factors which have now been physiologically relevant. Certain factors have been studied over the past few years including genetics, endothelial dysfunction, low birth weight and gestational feeding, and neurovascular abnormalities. Additional researches are necessary in order to clarify the association of immune cytokines with the nervous system, kidney, and vasculature and how it could be disturbed to provide therapeutic benefit. Also, further work is required to determine whether drugs that target hypertensive-linked pro-inflammatory cytokines, such as monoclonal antibodies, may become a new therapeutic choice in hypertension treatments.

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