

## Review Article

## Vascular Inflammation and Hypertension

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## Introduction

Hypertension is a major cause of morbidity and mortality worldwide. Over the past years, a plethora of information has established the diagnostic and prognostic value of various mediators of vascular inflammation in hypertension. However it is difficult to explain clearly what causes hypertension in human study. Many animal or *in vitro* models explain on the relation vascular inflammation and hypertension. This review focuses on the relation vascular inflammation and hypertension by the possible mediators, CRP (C-reactive protein), adaptive immune response, oxidative stress, RAS (renin-angiotensin-aldosterone system), prostaglandin, and Th17 activation by high salt intake (Figure 1).

## CRP (C - Reactive Protein)

CRP is considered the inflammatory marker with the strongest association with hypertension. It has been demonstrated in numerous clinical trials that hypertensive patients commonly have increased plasma CRP levels [1]. Nonhypertensive offspring of hypertensive parents tend to have higher serum CRP levels than offspring of nonhypertensive patients [2]. Elevated HS-CRP is both a risk marker and risk factor for hypertension and cardiovascular disease [3]. Increases in HS-CRP (over 3µg/mL) may increase blood pressure in just a few days in dose dependent fashion [4]. Increases in high sensitivity CRP (HS-CRP) as well as other inflammatory cytokines such as interleukin-1B, (IL-1B), IL-6, tumor necrosis alpha (TNF-α) and chronic leukocytosis are observed in hypertension and hypertension-related target organ damages, such as increased carotid intima media thickness (IMT) [5]. CRP is an acute phase protein, but it also can stimulate monocytes to release proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) and also acts on endothelial cells to express intracellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, these effects further promote

## Abstract

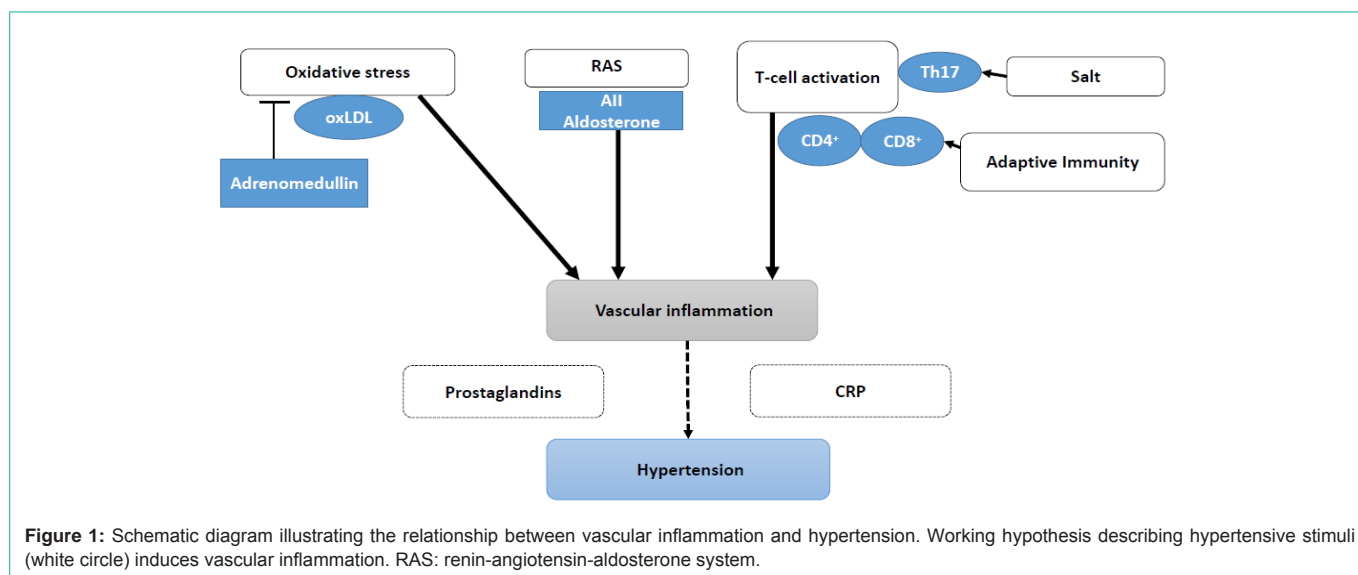
Hypertension is a very common disease and is often associated with left ventricular hypertrophy, obesity, diabetes and dyslipidemia. The consequences of hypertension involve coronary heart disease, heart failure, renal failure, stroke and exacerbation of the occlusive atherosclerotic coronary arterial disease. These disease states are associated with vascular structural and functional inflammatory changes including endothelial dysfunction, altered vasomotor tone, and vascular remodeling. However, whether vascular inflammation is a cause or result of hypertension is not well understood. Vascular inflammation and hypertension may share some common pathophysiological mechanism. In this review will show recent data concerning a potential link between inflammation and hypertension, including CRP, oxidative stress, RAS, prostaglandin, adaptive immune system, and Th17 activation by high salt intake, a major risk factor for developing hypertension.

**Keywords:** Oxidative stress; LOX-1; Adrenomedullin; Aldosterone; COX-2; Th17

inflammation. CRP is only marker for inflammation, what stimuli increases CRP and whether vascular inflammation increase CRP are not known.

## Oxidative Stress

In human hypertension, biomarkers of systemic oxidative stress are elevated [6,7]. CRP levels also have been shown to correlate with the level of oxidative stress in inflammatory cells from hypertensive patients [8,9]. Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase is a major source of ROS in immune cells and also in the vasculature. Excessive ROS levels can also induce cellular damage by interacting with DNA, lipids, and proteins, which may further impair vascular structure and function [10]. Reactive oxygen species (ROS) is defined as oxygen with unpaired electron and highly active chemical. Superoxide anion (O<sub>2</sub><sup>-</sup>), hydroxyl radical (HO•), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), peroxynitrite (ONOO<sup>-</sup>) and lipid radical are classified ROS [11]. In cellular matrix or membrane, in addition to NADPH oxidase, xanthine oxidase, cyclooxygenase, lipoxygenase, NO synthase, hemeoxygenase, peroxygenase, or heme protein are potential enzymes to produce ROS. In vascular endothelial cells, eNOS which is a cytochrome P450 reductase-like enzyme is important source for ROS. eNOS utilizes tetrahydropterin (BH4) to produce NO from L-arginine and under deficiency of L-arginine or BH4, eNOS produces O<sub>2</sub><sup>-</sup> or H<sub>2</sub>O<sub>2</sub>. Physiologically, ROSs are produced in a controlled manner at low concentrations and function as signaling molecules to maintain vascular integrity by regulating endothelial function and vascular contraction-relaxation balance. ROS activates Ca<sup>2+</sup> signal, tyrosine kinases or mitogen-activated protein kinases (MAPK) by non-genomic action and increases expression of MCP-1, VCAM-1, ICAM-1 and atherogenic genes by genomic action via activating NF-κB. Under pathological conditions, increased ROS bioactivity leads to vascular inflammation which is an essential pathophysiological mechanism in the development of hypertension.



### Oxidized LDL

Oxidized LDL is produced by oxidation of low density lipoprotein (LDL) and its oxidation is caused by peroxyradical and radical chain reactions. Source of ROS are leukocytes, macrophage, endothelial cells as well as vascular smooth muscle cells. Oxidized LDL increases MCP-1 secretion from endothelial cells and further induces monocyte and macrophage infiltration into vasculature [12]. Lectin-like oxidized low-density lipoprotein receptor (LOX-1) mRNA expression is minimal in the aorta from normotensive rats, but is markedly up-regulated in spontaneously hypertensive rats and salt-loaded Dahl salt-sensitive rats, suggesting a correlation between LOX-1 and hypertension [13]. However, there has been little information on the relationship between LOX-1 and hypertension in humans. In a study of healthy workers, serum LOX-1 ligand containing ApoB (LAB) level was correlated with only diastolic but not systolic blood pressure [14]. LOX-1 is also regulated by oxidative stress [15,16], and oxidized LDL induces ROS via LOX-1, therefore there are vicious cycles among ROS [17]. Cellular and organ damages by Oxidized LDL-induced ROS are not limited in endothelial cells but cardiomyocyte remodeling after ischemia or inflammation and fibrosis in the kidney [12].

### Adrenomedullin

The endogenous and exogenous antioxidants that have demonstrated an ability to alter the function of blood vessels and participate in the main redox reactions involved in vascular inflammation. Adrenomedullin (AM) was identified by Kitamura in 1993 as a potent vasodilating peptide [18] and the studies using its deficient mice model revealed that AM is a potent intrinsic antioxidant. Plasma adrenomedullin concentrations are elevated in many hypertensive patients [19]. In AM deficient mice, overall ROS marker, 8-isoprostaglandin F2 excretion is high and angiotensin II plus salt loading induced local ROS production in the heart and marked pericoronary fibrosis and narrowing independent from blood pressure [20]. In other model, cuff-induced vascular damage was reduced by topical administration of AM via viral vector and this effect was in parallel with reduction of ROS [21]. These models are closely related local or systemic renin-angiotensin system which

is a strong inducer of NADPH oxidase and oxidative stress. *In vitro* experiments showed that AM interfere with angiotensin II signaling and inhibits NADPH oxidase activity [22].

### Antioxidants and hypertension

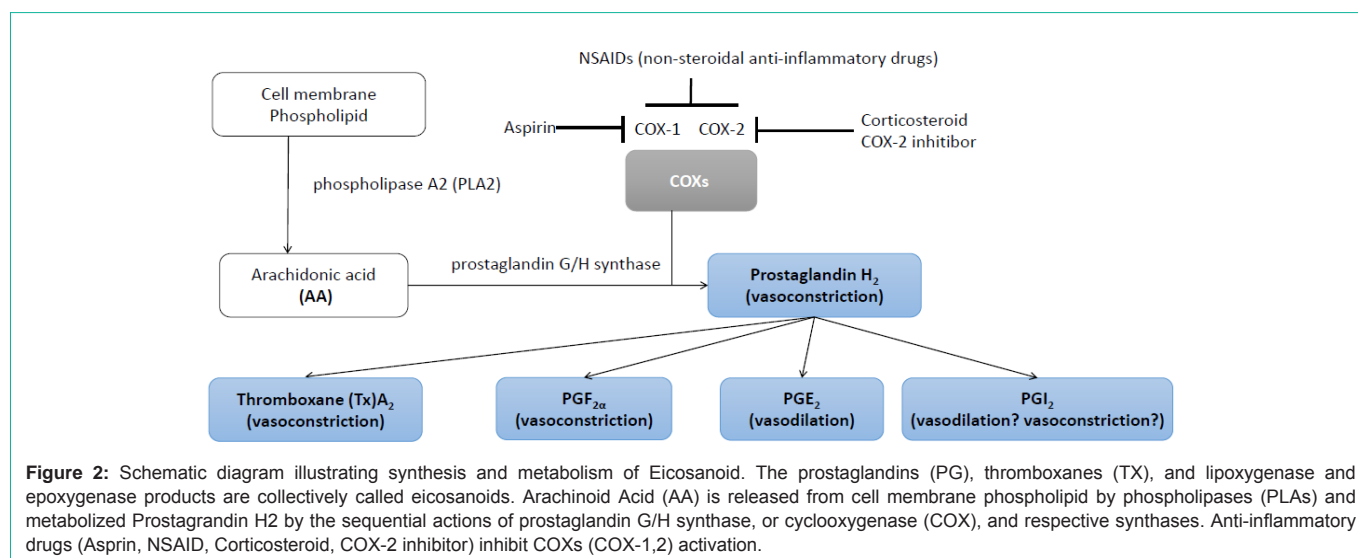
Antioxidants for hypertension are the study of, in which a peptide inhibitor of the NADPH oxidase was shown to lower blood pressure and to prevent macrophage accumulation [23]. Roson et al showed that the acute infusion of sodium caused an increase in renal levels of chemokine ligand 5 (RANTES), NFκB, HIF1a, and angiotensin II in rats, and that superoxide dismutase (SOD) mimetic, Tempol, markedly reduced these responses [24]. The above mentioned intrinsic antioxidants are scavengers and also exogenous antioxidants are studied for long time in human. Vitamin C is a potent water-soluble antioxidant. On the vascular wall behaves as enzyme modulator exerting up-regulation on eNOS and down regulation of NOX [25]. Nevertheless, there are several clinical trials in which the effect of vitamin C supplements on blood pressure have yielded inconsistent findings [26]. Recently cholesterol lowering drugs, probucol and statins are reported to have antioxidant property as their pleiotropic effects [27]. However, the dietary intake of antioxidants and polyphenols could have an effect in the primary prevention or reduction of hypertension. [28]. There are some reports that those exogenous ROS scavengers are effective in preventing hypertension, but there remain controversial reports [29].

### RAS (Renin-Angiotensin System)

Angiotensin II and Aldosterone are well known to the renin-angiotensin system (RAS), they are strongly inducer for vascular inflammation. RAS plays a crucial role in the initiation and maintenance of vascular inflammation and vascular remodeling [30]. Vascular inflammation leads to endothelium dysfunction. A dysfunctional endothelium is leaky and facilitates migration of inflammatory cell into the vascular wall and stimulates smooth muscle cells proliferation.

### Angiotensin II

More convincing support has been provided by the use of ACE



inhibitors in recent clinical trials in which profound effects of ACE inhibitors on reducing cardiovascular events were seen. Angiotensin receptor blockers (ARBs) may also reduce inflammation not only decrease blood pressure [31]. In animal model, acute treatment with Ang II significantly increases inflammatory changes, leukocytes adhesion in mesenteric arteries [32]. Moreover, animal and human studies show that Ang II induces proinflammatory responses in arteries, heart, and kidney by regulating the expression of cytokines and chemokines. Macrophages are components of the innate immune system, and are poised to respond to non-specific stimuli, such as might be present in the tissue damage induced by angiotensin II [33]. It is also now well-established that Ang II activates NADPH oxidases in VSMCs, monocytes, macrophages, and endothelial cells to produce reactive oxidant species [34]. In the setting of Ang II-induced hypertension, higher levels of subunit of NADHP oxidase expressions, including p47phox, p22phox, and NOX2, components of NOX2 oxidase. Furthermore, adoptive transfer of T cells deficient in NADPH oxidase results in lower superoxide production and blood pressure in response to Ang II [35].

### Aldosterone

Clinical studies indicate that the prevalence of hyperaldosteronism may be increased in resistant hypertension, that aldosterone concentrations “escape” to pretreatment levels during chronic treatment of congestive heart failure or hypertension with an Ang-converting enzyme (ACE) inhibitor or Ang receptor blocker (ARB) [36]. Seminal studies in rat models demonstrated that MR activation causes perivascular and interstitial fibrosis [37]. Rocha et al., demonstrated that treatment with aldosterone and salt caused extensive inflammatory arterial lesions with perivascular macrophages in the heart [38]. MR antagonism decreases aortic inflammation, fibrosis, and hypertrophy in hypertensive rats [39]. However, the heart and the vasculature do not have enough expression of 11β hydroxysteroid dehydrogenase type II, there are some reports the genomic activation by the mechanism of Aldo binds MR and expresses its pro-inflammatory action without glucocorticoid deactivation [40]. Despite lowering plasma aldosterone, salt worsens renal injury by paradoxical activation of the mineralocorticoid

receptor (MR) [41]. Fujita et al showed two pathways involving aldosterone-MR and renal SNS-GR that contribute to an impaired capacity to excrete sodium [42-44].

Like Ang II, aldosterone activates NADPH oxidases in rat VSMCs [45]. Increased oxidative stress activates the redox sensitive NF-κB, and triggers inflammation. Hence, aldosterone-stimulated activation of vascular inflammation by oxidative stress and NF-κB. Besides rac1, a component of NADPH oxidase, can translocate mineralocorticoid receptor into nucleus independent from aldosterone and exerts its genomic effect to induce its target gene transcription such as sgk1 [42]. This indicates that oxidative stress can activate mineralocorticoid receptor in organs even aldosterone level is low [46,47]. It implies that mineralocorticoid receptor blockade and reduction of salt intake are possibly effective in reducing inflammation and preserving vascular function in hypertensive patients [48].

### Prostaglandins

A number of animal studies and observations in human hypertensive subjects suggest that the prostaglandin system plays a role in the pathogenesis of hypertension. Inflammation activates phospholipase A2 (PLA2) to release Arachidonic Acid (AA), whose metabolism by cyclooxygenases (COXs) generates prostaglandins (PGs). PGs normally have an antihypertensive action. Prostacyclin (PGI<sub>2</sub>) inhibits platelet aggregation and vasoconstriction. PGI<sub>2</sub> synthase (PTGIS), a catalyst of PGI<sub>2</sub> synthesis from prostaglandin H<sub>2</sub>, is widely distributed and predominantly found in vascular endothelial and smooth muscle cells. However, PGH<sub>2</sub> (prostaglandin endoperoxide), thromboxane (Tx)A<sub>2</sub> generated by TxA<sub>2</sub> synthase (TxA<sub>2</sub>-), and isoprostanes (Iso) can constrict blood vessels [49] (Figure 2). Recent animal studies have shown that PGI<sub>2</sub> may, in fact, paradoxically induce vasoconstriction rather than vasodilatation in certain circumstances. In the aortic rings from SHR and aged Wistar Kyoto rats, the endothelium dependent contractions elicited by acetylcholine most likely involve the release of PGI<sub>2</sub> with a concomitant contribution of PGH<sub>2</sub> [50]. In previous studies, mice deficient in the prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) EP2 receptor is low in resting systolic blood pressure (BP) than that of wild-type controls

[51]. The BP of those mice increased blood pressure when they were put on a high-salt diet, suggesting that the EP2 receptor is involved in sodium handling in the kidney [52]. We analyzed three single-nucleotide polymorphisms (SNP) in the human PTGER2 gene the A/A type of the SNP rs17197 (rs17197, A/G in 3'UTR) was significantly more frequent in EH subjects than in NT subjects [53]. Synthesis of PGI<sub>2</sub> is enhanced in the spontaneously hypertensive and Goldblatt hypertensive rat [54]. We and other group identified several mutations in the human PGI<sub>2</sub> synthase (PTGIS) gene in a family with a history of essential hypertension, but haplotype of PTGIS genes were not associated in essential hypertension [55-62]. Metabolism of PGE<sub>2</sub>, PGF<sub>2</sub>-α, and PGI<sub>2</sub> by prostaglandin 15-hydroxydehydrogenase is impaired in hypertensive genetic models [63]. In either case, prostanoids cause both prohypertensive and antihypertensive effects by acting on blood vessels.

### COX inhibitors

Cyclooxygenase (COX) catalyzes the synthesis of prostaglandins (PGs) from arachidonate. The cyclooxygenase-derived prostanoids (e.g., PGE<sub>2</sub>, PGF<sub>2</sub>, PGD<sub>2</sub>, PGI<sub>2</sub>, thromboxane A<sub>2</sub>) are generated by either the largely constitutive isoform COX-1 or by the inducible isoform COX-2. Two isozymes encoded by different genes, *cox1* and *cox2*, mediate this process. Accumulating evidence indicates COX-1 and COX-2 activity differentially influence renal and cardiovascular function. For example patients receiving a selective COX2 inhibitor exhibited an increased incidence of thrombotic cardiovascular events and hypertension [64]. In addition to the well-recognized gastrointestinal toxicity caused by nonspecific COX inhibitor (NSAIDs), these agents have also been found to produce a mean increase in blood pressure of 5.0 mm Hg [65]. In contrast, low-dose aspirin, which primarily inhibits COX1, can lower blood pressure in healthy subjects with mild hypertension, [67,68]. Future studies are needed to assess the effect.

### Adaptive Immune Response

Several recent investigations have further defined the role of immune system. Particularly the adaptive immune system, in hypertension, provided novel insights into the genesis of hypertension, and identified novel targets for the treatment of hypertension [69]. The first line of defense against pathogens is the innate immune response. In contrast to the innate immune system, the adaptive immune system is highly specific. Grollman et al., showed that immunosuppression attenuates hypertension in rats [70]. Ba et al. found that transplanting the thymus from a Wistar-Kyoto (WKY) rat to a spontaneously hypertensive rat (SHR) resulted in a decrease in blood pressure in the SHR [71]. Based upon this finding, more in precise mechanism how immune responses by either T and B cells regulate blood pressure has been studied. Mice lacking recombinase-activating gene 1 (Rag-1<sup>-/-</sup> mice) cannot generate functional T cell receptors or B cell antibodies and thus lack both T and B lymphocytes [35]. The increase in blood pressure caused by either Ang II or DOCA salt was significantly blunted in Rag-1<sup>-/-</sup> mice, suggesting that either T or B cells mediate overt hypertension. Rag-1<sup>-/-</sup> mice did not exhibit increased vascular superoxide production and endothelial dysfunction. This results shows that T cells play a major role in hypertension. Several recent studies suggest a vascular protective effect of T regulatory cells, much in the same

way that these cells may provide renal protection [72]. An association between vascular inflammation and T regulatory cells was initially described in salt-sensitive hypertension by comparing vascular inflammatory markers and T cells in Dahl rats with chromosome 2 from the Brown Norway rat in which regulatory T cell function is suppressed by increased FOXP3. The congenic rats exhibited reduced vascular inflammation and increased vascular expression of Foxp3, a transcription factor specific to T regulatory cells [73]. In other study, either mineralocorticoid or AngII-dependent hypertension model, adoptive transfer of T regulatory cells blunts the hypertension and prevents the development of impaired mesenteric artery function and remodeling [74]. Immune cell in the conduit vessels might be an important factor for what is occurring in resistance vessels, especially the renal microvasculature, as a mechanism to promote the development of hypertension.

### T Cell Activation by Salt

The relevance of the renal inflammation in the pathogenesis of Salt Sensitive Hypertension (SHTN) is underlined by the demonstration that treatments that suppress the renal inflammation result in amelioration or prevention of salt-driven hypertension. The connection between sodium intake and health is manifested by the relationship between sodium intake and blood pressure. Several studies revealed salt sensitive animal models showed inflammation in the kidney and changed inflammatory gene expressions [75]. Salt-sensitive hypertension with increased renal inflammation as a result of T cell imbalance, dysregulation of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes and chronic leukocytosis with increased neutrophils and reduced lymphocytes [76].

Patients with hypertensive nephrosclerosis have higher renal infiltration of CD4<sup>+</sup> and CD8<sup>+</sup> T cells than normotensive control patients. Furthermore, circulating levels of chemokines have been reported to be elevated in hypertensive patients [77]. Pro-inflammatory cytokine Interleukin-17 (IL-17) contributes hypertension [78]. IL-17 is produced by Th17 cells. Two recent studies collectively suggest that excess sodium drives autoimmunity at the cellular level [79,80]. One group of researchers had showed increased Th17 cell numbers in the blood of people who consumed high salt diet, they conducted experiments on the effects of elevated sodium concentrations on the differentiation of immature human T cells into pathogenic Th17 cells. They indeed found that high sodium concentrations drove a dramatic increase in differentiation into pathogenic Th17 cells in vitro. To strengthen these findings, they fed mice predisposed to a Th17-related autoimmune disease either a standard or high-salt diet. The high-salt diet accelerated the development of the autoimmune disease, and the symptoms were more severe on the high-salt diet than on the standard diet.

### Conclusion

The recent studies have shown the relevance of inflammation and hypertension, including its mediators. C-Reactive Protein (CRP) is considered the inflammatory marker with the strongest association with hypertension. Oxidative stress, RAS are known to be associated with inflammation and can contribute to hypertension. T-cells activation at least in part elevate blood pressure by exacerbating autoimmune response in vasculature and possibly in the kidney.



However, some anti-inflammatory drugs (NSAID or COX-2 inhibitor) paradoxically cause hypertension in human. Because immunosuppressants can have serious side effect (such as sodium retention, inhibit angiogenesis). Clinical studies investigating anti-oxidant supplements have failed to show any consistent benefit. Most clinical studies on anti-oxidants were not enough to scavenge oxidative stress and it also become free radical in body, if there were pro-oxidant conversion. New anti-inflammatory drugs could be used for prevent hypertension, or vascular inflammation in future.

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