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REVIEW Article

The Rennin-Angiotensin-Aldosterone System (RAAS) in Vascular Inflammation and Remodeling

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ABSTRACT

The renin-angiotensin-aldosterone system (RAAS) through its physiological effectors plays a key role in promoting and maintaining inflammation. Inflammation is an important mechanism in the development and progression of cardiovoascular diseases (CVD) such as hypertension and atherosclerosis. In addition to its main role in regulating blood pressure and therefore its role in hypertension, RAAS has pro-inflammatory and profibrotic effects at cellular and molecular levels. Blocking RAAS provides beneficial effects for the treatment of cardiovascular and renal diseases. Evidence shows that inhibition of RAAS positively influences vascular remodeling thus improving vascular disease outcomes. The beneficial vascular effects of RAAS inhibition are likely due to decreasing vascular inflammation, oxidative stress, endothelial dysfunction, and positive effects on regeneration of endothelial progenitor cells (EPC). Inflammatory factors such as vascular cell adhesion molecule-1 (ICAM-1), tumor necrosis factor-α (TNFα), interleukin-6 (IL-6), and C-reactive protein (CRP) have key roles in mediating vascular inflammation, and blocking RAAS negatively modulates the levels of these inflammatory molecules. Some of these inflammatory markers are clinically associated with cardiovascular disease events. More studies are required to establish long-term effects of RAAS inhibition on vascular inflammation, vascular cells regeneration, and cardiovascular disease clinical outcomes. This review presents important information on RAAS's role on vascular inflammation, vascular cells responses to RAAS effectors, and on inhibition of RAAS signaling in the context of vascular inflammation, vascular remodeling, and vascular inflammation-associated CVD. Nevertheless, the review also equates the need to re-think and re-discover new RAAS inhibitors.

Keywords:
vascular inflammation, vascular remo-deling, rennin - angiotensin - aldosterone system, inhibitors

Abbreviations

Angiotensin (ANG); Angiotensin converting enzyme (ACE); Angiotensin receptor blockers (ARB); C-reactive protein (CRP); Cardiovascular disease (CVD); Direct rennin inhibitors (DRI); Endothelial progenitor cells (EPC); Extracellular receptor kinase (ERK); Epidermal growth factor receptor (EGFR); Endothelial nitric oxide synthase (eNOS); Endothelium-derived hyperpolarizing factor (EDHF); Endothelin 1 (ET-1); Interleukin 1 beta (IL-1β); Interleukin 6 (IL-6); Intracellular cell adhesion molecule 1 (ICAM-1); Insulin growth factor (IGF); Monocytes chemoatractant protein 1 (MCP-1); Monocytes inflammatory protein 1 (MIP-1); Mineralo-corticoid receptor antagonist (MRA); Nuclear factor kappa B (NF-κB); Nitric oxide (NO); Peroxisome proliferators-activated receptor gamma (PPARγ); Renin-angiotensin-aldosterone system (RAAS); Transforming growth factor beta (TGFβ); Tumor necrosis factor alpha (TNFα); Vascular cell adhesion molecule 1 (VCAM-1);

SUMMARY

1. Renin-angiotensin-aldosterone system (RAAS) and cardiovascular disease

The rennin – angiotensin - aldosterone system (RAAS), one of the most important hormonal system, oversees the functions of cardiovascular, renal, and adrenal glands by regulating blood pressure, fluid volume, sodium and potassium balance [1]. The classical RAAS system was discovered more than a century ago, and in 1934 Harry Goldblatt showed a casual link between kidney function and blood pressure [2]. Since then, extensive experimental studies have been undertaken to identify the components of the RAAS, and its role in regulating blood pressure. Abnormal activity of the RAAS leads to the development of an array of cardiovascular diseases (CVD; hypertension, atherosclerosis, left ventricular hyperthrophy), cardiovascular events (myocardial infarction, stroke, congestive heart failure), and renal disease [1]. As early as in 1956, Leonald T. Skeggs suggested the development of drugs to regulate renin-angiotensin-system, and since then an array of inhibitors have been developed. Owing to a higher RAAS signaling pathways complexity than previously thought, half-century later, new RAAS inhibitors are still being developed [3]. Indeed, numerous experimental and clinical evidences indicate that pharmacological inhibition of RAAS with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), direct rennin inhibitors (DRIs), and mineraclocorticoid receptor antagonists (MRAs) is effective in treating hypertension, diabetic renal injury, and the results show a reduction in CVD events and heart failure world-wide [1]. This review is focused on the role of RAAS components and its modulatory effects on inflammation and vascular remodeling.

1.1 RAAS

Renin, an active proteolytic enzyme, is first synthesized as an inactive preprohormone (prorenin), undergoes subsequent proteolytic changes in the afferent arterioles of renal glomerulus and then is released into circulation [4]. In the circulation, proteolytic and nonproteolytic mechanisms cleave prorenin to the active renin. Active renin acts upon its substrate, angiotensinogen, to generate angiotensin I (Ang I). Ang I is cleaved by angiotensin-converting enzyme (ACE) resulting physiologically active angiotensin II (Ang II). Ang II, the main effector of the RAAS, mediates its effects via type 1 Ang II receptor (AT1R). However, few studies suggest the existence of additional receptors for prorenin and renin in the heart, kidney, liver, and placenta [5]. Other studies suggest the presence of renin receptors in visceral and subcutaneous adipose tissues suggesting a local production of Ang II. Activation of prorenin and renin receptors stimulates mitogen activated kinase (MAPK)/ extracellular signal-regulated kinase (ERK1/2) related signaling pathway [6]. Since the rate-limiting step of RAAS is under the control of renin, the idea of inhibiting renin to suppress RAAS was suggested in the mid 1950s, but the development of rennin inhibitors was a long and difficult process [7]. Likewise, the first oral DRI, aliskiren, was marketed in 2007 for the treatment of hypertension [8]. Another effector of the RAAS, aldosterone, exerts important endocrine functions by regulating fluid volume, sodium and potassium homeostasis, and primarily acting in the renal distal convoluted tubules. Aldosterone mediates genomic and non-genomic effects via mineralocorticoid receptor (MR), AT1R, G-protein-coupled receptor, and epidermal growth factor receptors (EGFR). Downstream effectors of these receptors such as MAPK/ERK1/2 pathway mediate vascular biology and physiology, particularly, vascular remodeling, inflammation, fibrosis, and vascular tone. Aldosterone's cardiopathological effects include myocardial fibrosis and hypertrophy, and vascular remodeling and fibrosis. Production of aldosterone is under the regulation of angiotensin II, hyperkalemia, adrenocroticotropic hormone

(ACTH), and sodium level [9]. Clinical trials have shown that blocking aldosterone receptors with mineralocorticoid receptor anatagonists (MRA) spironolactone or eplerenone reduces blood pressure, lowers albuminuria, and improves the outcome of patients with heart failure or myocardial infarctions, or cardiovascular complications associated with diabetes mellitus [10]. Aldosterone infusion in an ischemia animal model induces vascular changes via AT1R, since blocking AT1R inhibited aldosterone effects, indicating cross-talk among RAAS components.

The recent discovery and cloning of a new angiotensin converting enzyme, ACE2, has introduced further complexity to RAAS. ACE2 is 42% homolog to ACE1, and is expressed in the heart, kidney, testis, endothelium of coronary, intrarenal vessels, and renal tubular epithelium [11]. ACE2 is a monopeptidase with enzymatic preference for hydrophobic/basic residues of Ang II C-terminus that leads to the formation of angiotensin II (1-7). Experimental studies show that Ang II (1-7) is a competitor of Ang II, and indeed may have cardio-renal protective effects [12, 13]. Ang II is also produced by non-ACE enzymes, such as serine protease chymase, which have been found in the heart, vasculatures, and other tissues [14, 15].

2. Inflammation and cardiovascular disease

Inflammation plays a key role in the initiation, progression, and development of an array of cardiovascular diseases such as hypertension, atherosclerosis, restenosis after balloon angioplasty, nephropathy, and cardiomyopathy [16]. A typical example of how inflammation underlies the development of cardiovascular disease is atherosclerosis, via the activation of endothelial cells by the inflammatory cytokines. Endothelium dysfunction due to injury by the inflammatory process has been associated with cardiovascular risk factors including hypertension, diabetes mellitus, or obesity [17].

2.1 Markers of inflammation

Tumor necrosis factor alpha (TNFα) is a key proinflammatory cytokine regulating the expression of many genes of inflammation, oxidative stress, and anti-apoptotic signaling pathways, virtually, in all types of cells [18]. Aberrant TNFα signaling leads to the development of pathological conditions, including cardiovascular disease. Therapeutic blocking of TNFα signaling has been proposed for the treatment of several inflammatory diseases, particularly rheumatoid arthritis and bowel disease [18]. TNFα impairs endothelium-dependent nitric oxide (NO) mediated vasorelaxation in coronary arteries or carotid artery via superoxide radical production [19]. Patients with high levels of circulating TNFα have a greater risk in developing cardiovascular disease [21]. In endothelial cells, TNFα induces the expression of interleukin-6 (IL-6), monocyte chemoatractant protein-1 (MCP-1), and cell adhesion molecules (CAM) [20]. In mice, deletion of TNFα inhibits intimal hyperplasia after carotid artery injury [23], while an increased expression of TNFα aggravates pulmonary hypertension [24]. TNFα mediated inflammation plays an important role in vascular remodeling. Human carotid artery smooth muscle cells respond to TNFα with increased cell proliferation, whereas inhibition of circulating TNFα prevents carotid artery post-injury media remodeling and neointima formation in rats [22]. TNFα inhibition has been shown to improve endothelium function via stimulating endothelial cells regeneration [25].

NF-κB, a pro-inflammatory factor down-stream of TNFα, plays a central role in regulating the expression of vascular inflammatory mediators interleukin-1beta (IL-1β), interleukin-6 (IL-6), TNFα, MCP-1 in endothelial cells and other cell types [26]. Activated NF-κB induces vascular smooth muscle cells proliferation and mediates neointimal hyperplasia after vascular injury [27].

Another marker of inflammation is C-reactive protein (CRP). CRP is considered a hallmark of the acute-phase response and a predictor of cardiovascular event risk [28]. C-reactive protein is mainly produced in the liver [29], but other cell types, such as smooth muscle and endothelial cells, of atherosclerotic arteries show CRP expression [30]. CRP plays a role in mediating vascular disease. In vitro studies show that CRP has pro-inflammatory and pro-thrombotic effects [31], inhibits endothelial progenitor cell differentiation and function [32], and up-regulates AT1R [33]. CRP activates classical complement signaling cascade, which plays a key role in neointima formation in injured vessels [34]. Circulating CRP levels correlate with several inflammation markers, including inflammatory cytokines, cell adhesion molecules, markers of activated platelets, and white

cells [35]. All of these inflammation markers are also predictive of coronary artery events [36].

Interleukin-6, a pleiotropic cytokine, regulates many cellular functions, including proliferation and apoptosis. IL-6 plays an important role in inflammation, and modulates the development of several diseases including cardiovascular diseases, such as hypertension and other related disease. High circulating levels of IL-6 are found in hypertensive patients. Type I diabetic rats have high circulating levels of IL-6, and increased blood vessel contractility [37]. IL-6 overexpression in mice induces pulmonary vascular remodeling that is similar to that seen in patients with pulmonary hypertension, and induces pulmonary hypertension via proliferative and antiapoptotic mechanisms [38]. IL-6 also modulates vascular reactivity. Treatment of isolated human blood vessels from various organs with IL-6 results in increased contraction [39]. IL-6 mediates the development of vascular occlusive disease and is a predictor of cardiovascular sudden death [40]. IL-6 effects on vascular system are mediated via NF-κB signaling, which plays a key role in vascular remodeling. Inhibition of NF-κB via deletion of IκBNS, a nuclear IκB regulatory protein of NF-κB, reduces intimal hyperplasia after vascular injury in mice via NF-κB-mediated IL-6 production [41].

2.2 Intercellular adhesion molecules

Inflammation-mediated injury to endothelium generates a pro-inflammatory signaling cascade and the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), both of which recruit blood monocytes to vascular wall, thus perpetuating the release of more cytokines and chemokines at injury site, culminating with the development of vascular disease, such as atherosclerosis. Circulating levels of ICAM-1 and VCAM-1 positively correlate with carotid intima-media ratio [42]. VCAM-1 expression is up-regulated by Ang II in rat aorta, whereas spironolactone, an antagonist of mineralocorticoid receptors, inhibits expression of VCAM-1 and of other inflammatory markers [43]. Treatment of endothelial cells with Ang II up-regulates VCAM-1 via oxidative stress and NF-κB activation [44]. High circulating levels of ICAM-1, VCAM-1, and other inflammatory cell adhesion molecules are associated with left ventricle hypertrophy (LVH) and diastolic dysfunction in aged population. [45]

3. RAAS and vascular inflammation

RAAS plays a crucial role in the initiation and maintenance of vascular inflammation and vascular remodeling. Vascular inflammation leads to endothelium dysfunction, and a decreased endothelial function mediates progression of cardiovascular disease. A dysfunctional endothelium is leaky, facilitates migration of inflammatory cells into the vascular wall and stimulates smooth muscle cells proliferation, processes that decrease vascular function and promote development of cardiovascular disease and tissue injury. A dysfunctional endothelium provides a pro-inflammatory environment promoting recruitment and attachment of inflammatory cells, which are well known to play a key role in atherosclerosis. There is increasing evidence indicating a link between hypertension and atherosclerosis via Ang II mediated inflammation. In vivo, acute treatment with Ang II significantly increases leukocytes adhesion in the rat mesenteric arteries [46]. Animal and human studies show Ang II has proinflammatory responses in arteries, heart, and kidney by regulating the expression of cytokines and chemokines. In human vascular smooth muscle cells, Ang II induces NF-κB activation and the expression of IL-6 [47], MCP-1, and TNFα in monocytes [48]. In vivo infusion of Ang II causes increased expression of VCAM-1 in rat aorta via NF-κB transcriptional activation. Administration of losartan, an AT1R antagonist, inhibits Ang II- induced NF-κB activation and VCAM-1 accumulation [49]. In vitro treatment of rat vascular smooth muscle cells with Ang II up-regulates MCP-1, and blockade of AT1R with losartan prevents MCP-1 expression and monocytes migration into vessel wall and other target organs [50]. Although a vasoconstrictor, Ang II induces endothelial damage by inhibiting endothelial cells regeneration. Ang II acts as a second messenger to activate intracellular signaling pathways, such as mitogen-activated protein kinase (MAPK) and AKT, pathways that mediate cell proliferation and inhibit apoptosis, thereby influencing vascular dysfunction [52]. Ang II plays a significant role in the initiation and progression of atherogenesis, an inflammation mediated process. In injured arteries, Ang II provides a positive feedback loop in vascular

inflammation via recruitment of inflammatory cells, which then produce more Ang II, therefore perpetuating vascular inflammation [1]. Ang II is a potent pro-oxidant. Ang II induces the production of superoxide anions and activates the pro-oxidant NADH/NADPH signaling [53]. Ang II-mediated oxidative stress reduces nitric oxide (NO) level, and activates redox sensitive genes, particularly cytokines, adhesion molecules, and matrix metalloproteinases [54]. Ang II is also a pro-fibrotic factor. Chronic infusion of mice with Ang II results in increased blood pressure, infiltration of inflammatory cells into myocardium, and cardiac fibrosis [55]. In rat cardiomyocytes, Ang II induces calcium signals (Ca2+), and oxidative stress, which cooperatively induce cardiomyocytes hypertrophy [56]. Chronic treatment of rat aortic smooth muscle cells with Ang II induces cell hypertrophy by increasing protein synthesis [57]. AngII-treated rat cardiac fibroblasts display increased expression of focal adhesion kinases (FAK) and integrins, whereas cardiac myocytes express high levels of c-fos, EGFR1, TGF-β, and extracellular matrix proteins (109, 110). Inflammation mediates endothelial injury, which alters endothelial cell architecture so that the endothelium becomes dysfunctional. It has been shown that a dysfunctional endothelium is directly associated with hypertension and atherosclerosis [17]. A functional endothelium is a key regulator of NO release, and loss of NO bioavailability is associated with high level of Ang II via oxidative stress. Although development of atherosclerosis is a multifactorial complex process, interaction between endothelial dysfunction and oxidative stress plays an important role in atherosclerotic process. Increased oxidative stress within the vascular wall is a hallmark of vascular disease, such as atherosclerosis, hypertension, and diabetes. Indeed, high level of superoxide is an important factor in atherosclerosis initiation by recruitment of inflammatory cells and endothelial dysfunction. Total genetic deletion of NADPH oxidase subunit Nox2 in mice results in significant decrease of aortic atherosclerosis [58]. Blocking RAAS with valsartan in combination with fluvastatin (a statin) in atherosclerosis mouse model, the apolipoprotein E (ApoE-/-) null mice, reduces the level of atherosclerotic lesions, superoxide anion, and the expression level of MCP-1 and ICAM-1, indicating that blocking inflammation and oxidative stress has beneficial effects on endothelium [59]. Indeed, clinical studies show a reduction in cardiovascular events beyond lowering blood pressure, such as positively altering endothelium/vascular wall structure, which in turn mediates reduction of cardiovascular disease. Several RAAS inhibitors such as ACEI ramipril and ARB losartan improve endothelial activity and vascular function by increasing NO bioavailability [17]. NO has protective effects on cardiovascular and renal systems. NO effects on the vasculature are numerous, from inducing vasodilation of all types of blood vessels to inhibiting platelet aggregation and adhesion or leukocytes adhesion to endothelium. Furthermore, NO inhibits DNA synthesis, mitogenesis, vascular smooth muscle cells proliferation, and counteracts oxidative stress [60]. NO bioavailability depends on the activity of eNOS, and a diminished eNOS activity is associated with essential hypertension [60].

The proinflammatory and profibrotic effects of the RAAS are also mediated by aldosterone. Aldosterone plays a role in organ fibrosis and tissue ischemia, and in conjunction with macrophages induces cardiac fibrosis [61]. Aldosterone promotes insulin resistance and vascular remodeling, influencing the development of atherosclerosis [62]. In vascular smooth muscle cells, aldosterone alters insulin signaling by up-regulating the expression of insulin-like growth factor-1 receptor (IGF1R) and hybrid receptor, and modulates membrane structure via tyrosine kinase receptors [63]. Chronic infusion of aldosterone induces oxidative stress in rat aorta, and MR antagonist spironolactone reduces reactive oxygen species generation [63]. Animal studies also indicate an association between aldosterone and decreased NO synthesis and endothelial progenitor cells (EPC) via oxidative stress and low levels of VEFGR2 [64]. NO plays a key role in vascular homeostasis through its effects on endothelial and smooth muscle cells. In endothelial cells, NO potentiates VEFG mitogenic effects thereby stimulating endothelial cells proliferation. In VSMC, NO limits their proliferation and migration [65]. In addition to RAAS present in systemic circulation and its production in local tissues, there are also reports on the identification of an intracellular RAAS in certain cell types such as hepatoma cells [66], renal cortical cells [67], or adrenal medullary chromaffin, and pituitary glandular cells [68]. Human and rat adrenal cortical

cells stimulated with Ang II produce aldosterone via AT1R-upregulation of cytochrome P450 oxidase B2 and increased level of hydrogen peroxide, whereas pretreatment with losartan and antioxidants abrogates Ang II effects [69]. As shown in Figure 1, AngII, the master cytokine, TNFα, and aldosterone, induce the expression of a myriad of molecular effectors of signaling pathway associated with vascular inflammation and remodeling, fibrosis, and oxidative stress. Several molecular molecules such as ERK1/2 and NADPH are also activated by AngII and aldosterone and activate NF-κB-dependent signaling in the absence of TNFα, cross-talk that indicates the complexity of RAAS effectors role in mediating vascular inflammation and remodeling (Figure 1). Moreover, the cross talk between AngII and aldosterone indicates the intricacy of the RAAS system on cardiovascular system pathology.

4. RAAS blockers and vascular inflammation

Blocking RAAS signaling either with ACEIs which inhibit the formation of angiotensin, or ARBs which block angiotensin receptors, or DRIs which inhibit the renin-angiotensinogen reaction, or MRAs which block aldosterone, alone or in combinations, reduces mortality and morbidity in diabetes, hypertension, atherosclerosis, heart failure, and stroke [70]. The multiple biological and physiological effects as a result of RAAS inhibitors are summarized in Figure 2 and include decreased inflammation, vascular remodeling, and fibrosis, oxidative stress, increased endothelial function and nitric oxide, and maintenance of bradykinin, and endothelium-derived hyperpolarizing factors (EDHF), which contribute to maintenance of vascular tone. However, blockade of the RAAS at one level is not highly effective to treat hypertension, therefore blocking RAAS at multiple levels seems to provide clinical efficacy for the treatment of hypertension and other forms of cardiovascular disease, including atherosclerosis [70].

4.1 Direct Renin Inhibitors (DRIs)

DRIs block RAAS by inhibiting renin enzymatic activity. A recently approved DRI, aliskiren, is an oral direct renin inhibitor that lowers blood pressure by blocking the rate-limiting step of the RAAS. In a randomized double-blinded trial study, Andersen et al. [71], and others [72] reported that aliskiren-based therapy lowered blood pressure (BP), and plasma renin activity (PRA), and the effects persisted over four weeks, suggesting long term effects of aliskiren on renin activity. However, plasma renin activity can be increased by ACEIs or ARB, therefore combination of aliskiren with an ACEIs or ARBs has been considered as a preferred option of treatment of hypertension, congestive heart failure, and chronic kidney disease [73]. Aliskiren has beneficial effects on endothelium. In patients with type I diabetes, aliskiren improved endothelial function independently of lowering blood pressure. In an atherosclerosis transgenic mouse model, aliskiren alone or in combination with atorvastatin inhibited atherosclerosis development and plaque progression via decreasing monocytes adhesion and MCP-1 levels [74].

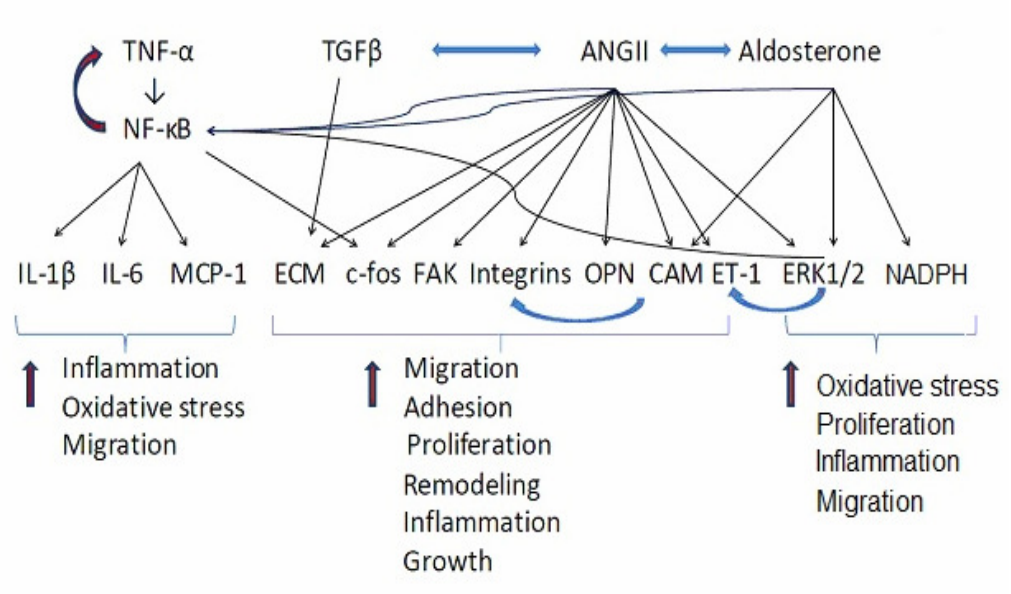

Figure 1:
Schematic representation of various molecular factors activated by RAAS effectors and cross-talk between RAAS effectors molecular factors involved in signaling pathways with role in vascular inflammation and remodeling. Abbreviations: single arrow: increased expression or stimulation.

In eNOS deficient mice, aliskiren prevented cardiac hypertrophy, inflammation, coronary artery remodeling, and vascular intimal hyperplasia, and even greater effects were found in combination with valsartan. Mechanistically, aliskiren and valsartan combination downregulates NADPH oxidase activity, therefore attenuates oxidative stress [60], which plays a key role in initiating the development of vascular inflammation and cardiovascular disease.

4.2 Angiotensin Converting Enzyme Inhibitors (ACEIs)

The use of ACEIs is an effective conventional treatment of hypertension, reducing left ventricular hypertrophy, therefore improving CV outcomes [75]. ACEIs treatment of patients with a dysfunctional endothelium caused by various pathological conditions improve endothelial functions measured by brachial flow mediated vasodilation (FMD) [76]. Mechanistically, ACEIs improve endothelium function by increasing NO level via blocking bradykinin degradation, and inhibit the production of endothelin-1 (ET-1), and Ang II by endothelium [77]. Maintaining bradykinin level has an additive effect on endothelium by increasing the level of prostacyclin [78], and endothelium-derived hyperpolarizing factor (EDHF) [79], both of which induce vasodilation, and inhibit vascular smooth muscle cells proliferation and platelet adhesion [77].

4.3 Angiotensin Receptors Blockers (ARBs)

Blockade of RAAS with ARBs has been shown to reduce inflammation and to improve endothelial function. In vitro and in vivo studies demonstrate that anti-inflammatory effect of ARB candesartan is through the suppression of the inflammatory receptors toll-like receptor 2 and 4 (TLR2 and TLR4) [17]. Indeed, TLRs have been implicated in development and progression of cardiovascular disease. In animal models of hypertension, TLR4 contributes to blood pressure regulation and small resistance arteries vasoconstriction [80]. In hypertensive patients, ARB irbesartan has been shown to improve endothelial function and vascular reactivity, and to reduce the levels of CRP, ICAM-1, IL-6, and oxidative stress marker 8-isoprostane [81]. It is well known that oxidative stress plays an important role in mediating endothelium dysfunction. Use of valsartan has been shown to prevent the formation of reactive oxygen species (ROS), and to suppress the activity of NF-κB, a transcription factor that regulates the expression of inflammatory cytokines and cell adhesion molecules, all of which contribute to development of vascular inflammation and of vascular events [82]. In vitro and in vivo studies have shown that ARB olmesartan inhibits Ang II-induced aortic vascular smooth muscle cells migration, therefore prevents vascular remodeling [83].

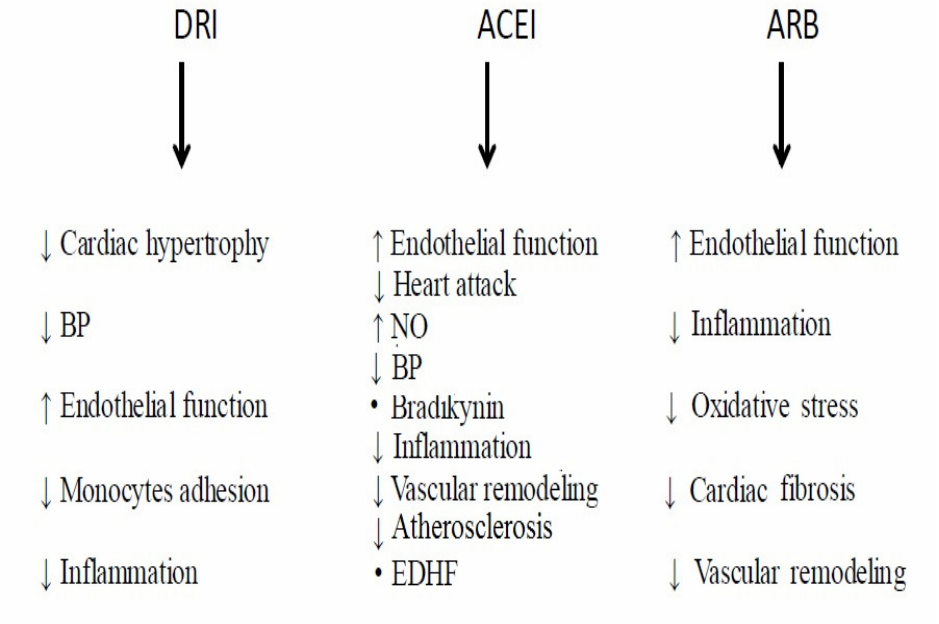

Figure 2:
Schematic representation of RAAS inhibitors on cardio-vascular function. Angiotensin - converting enzyme inhibitors (ACEI); type 1 Ang II receptor blockers (ARB); blockers (MRB); direct rennin inhibitors (DRI). Thick arrow: stimulation; thin arrow: increased or decreased; bullet: no change

Use of ARBs in patients with type 2 diabetes mellitus or with stable coronary artery disease increases the number of cardioprotective and endothelial progenitor cells [84, 85].
ARBs exert beneficial effects for the treatment of coronary disease and atherosclerosis. Lorsartan treatment improves flow-mediated coronary artery disease in patients with atherosclerosis and endothelial function via NO bioavailability.

4.4 Mineralocorticoid receptor antagonists

Dysregulated mineralocroticoid system signaling influences hypertension, atherosclerosis, and cardiac failure independent of renal MR actions on blood pressure [86]. Aberrantly activated MR negatively modulates endothelium function in patients with cardiovascular risk factors and disease. MR are present in vascular smooth muscle cells, endothelial cells, and cardiomyocytes [87]. Activation of MR induces oxidative stress [88], inhibits vascular relaxation, and induces vascular inflammation, fibrosis, and remodeling [63]. Aldosterone-activated MR in human endothelial cells (EC) induces the expression of inflammatory factor ICAM-1 and leukocytes-EC adhesion, and blocking MR with spironolactone inhibits aldosterone-mediated effects on EC [88]. Aldosterone impairs EPC differentiation, migration, and proliferation, whereas pharmacological inhibition or genetic manipulation rescues EPC functions [89, 90]. Aldosterone antagonist spironolactone improves endothelium-dependent vasodilatation via inhibition of NAD(P)H oxidase pathway [90]. Blocking aldosterone signaling also improves heart muscles proliferation and arterial wall remodeling, endothelial function, and NO synthesis [61]. Many clinical studies have shown that pharmacological inhibition of MR decreases the incidence of heart attack, stroke, and mortality in addition to lowering blood pressure [87]. Most recent studies also show additional benefits from blockade of aldosterone signaling, particularly decreased inflammation, reduced cardiovascular remodeling, and a reduction of atherosclerosis [61].

5. RAAS and vascular remodeling

Ang II also induces vascular remodeling, thrombosis, and plaques rupture [51, 91]. Ang II mediated vascular remodeling takes place via the expression of autocrine growth factors basic fibroblast growth factor (bFBS), transforming growth factor-β1 (TGF-β1), and insulin growth factor (IGF) [92]. Vascular remodeling mediated by Ang II is due to increased vascular cell migration, and modification of extracellular matrix composition [83, 93]. Changes in the structure and function of blood vessels, especially in small resistance blood vessels, potentiate the complications of hypertension. Moreover, remodeling of small blood vessels occurs before left ventricular hypertrophy, carotid artery intima-media thickening, or increases microalbuminuria levels. Indeed, a smaller lumen and external diameter of small resistance arteries is seen in patients with hypertension [94]. Changes in the function of small arteries are associated with decreased levels of vasodilators and increased sensitivity to Ang II and related signal transduction pathways.

In addition to its role in hypertension, the renin-angiotensin-aldosterone system also plays an important role in mediating vascular remodeling in neointimal hyperplasia after angioplasty and atherosclerosis [95-97]. Ang II is also a growth factor that regulates cell proliferation and differentiation, hypertrophy and apoptosis. In vascular remodeling, Ang II-induced remodeling effects are due to vascular smooth muscle cells proliferation and hypertrophy. The Ang II growth effects, proliferation vs hypertrophy are dependent on cell type and cell-cycle regulated genes. For example, Ang II exerts hypertrophic effect on cardiomyocytes via TGFβ1 mediated signaling, and blockade of TGFβ1 receptor abrogates Ang II-mediated cardiomyocytes hypertrophy [98]. In myocardial infarction model (MI), ARB, telmisartan, inhibits cardiac remodeling by reducing cardiomyocytes hypertrophy and fibrosis via an anti-inflammatory effect and activation of peroxisome proliferators-activated receptor gamma (PPARγ) [99]. The role of systemic and local renin-angiotensin system in vascular remodeling diseases, such as atherosclerosis and neointima hyperplasia after angioplasty, is well established [100]. Ang II/AT1R activation within vascular tissue leads to accumulation of inflammatory cells, fibrosis, and migration of vascular smooth muscle cells [101]. Blocking of Ang II signaling via ACEIs or ARBs have been shown to inhibit Ang II-mediated endothelial dysfunction and atherosclerosis [102], and ARBs efficiently inhibited vascular remodeling and neointimal hyperplasia after vascular injury

[103, 104]. Indeed, ARB telmisartan has been shown to suppress neointimal hyperplasia after heart transplant in a mouse model, suggesting that telmisartan might provide positive effects in preventing graft rejection [105]. ARB lorsartan has been shown to decrease intima:media ratio of carotid artery or result in arterial resistance in hypertensive patients, and to prevent the production of TGFβ, a known mediator of Ang II [106, 107]. Aldosterone plays a key role in cardiac fibrosis and remodeling via direct effects on collagen synthesis and deposition in the cardiac interstitium. Use of spironolactone in a rat model of myocardial fibrosis prevents myocardial fibrosis [108]. Therefore, all these results prove that blocking RAAS signaling positively regulates vascular remodeling, and vascular inflammation (Fig. 2).

6. Perspective on RAAS inhibition

Although RAAS system has been studied for more than a century, new experimental and clinical evidences suggest that the physiology of RAAS is complex and multifactorial, and new or on-going research will provide a better understanding on RAAS physiology. For example, the current understanding on how the interactions between Ang II and aldosterone regulate deleterious cellular processes indicates the intricacy of RAAS signaling and provides the basis for blocking RAAS at different levels (Fig. 2). Moreover, identifying novel targets/effectors of the RAAS system perhaps will provide the basis for the development of novel therapeutic strategies aimed at preventing vascular inflammation and remodeling, therefore improving the outcome of vascular disease.

Acknowledgements & Conflict of interest

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