Role of the Renin-Angiotensin-Aldosterone System and Proinflammatory Mediators in Cardiovascular Disease

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Inflammation is a key mechanism in the initiation, progression, and clinical sequelae of cardiovascular diseases (CVDs), including atherosclerosis, nephropathy, and cardiomyopathy. Angiotensin II, the major effector peptide of the renin-angiotensin-aldosterone system (RAAS), plays a significant role in the advent and perpetuation of these inflammatory diseases, most notably in atherogenesis. Consequently, suppression of the influence of angiotensin II by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may reduce or potentially reverse atherosclerosis and other inflammation-associated CVDs. Angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors exert anti-inflammatory actions and prevent or reduce the development of atherosclerosis in animal models. Clinically, RAAS suppression reduces common carotid and femoral artery intima-media thickness, thus indicating moderation of the vascular disease process. These clinical benefits likely involve restraint of the deleterious effects of angiotensin II in addition to, or independent of, lowering blood pressure. Increasing evidence that the detection and monitoring of vascular inflammation are important tools in the management of atherosclerosis also implicates the RAAS in this pathogenic process. Inflammatory molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, tumor necrosis factor-α, and C-reactive protein have potential diagnostic and prognostic values in CVD and are modified by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Monitoring these markers may be crucial for determining which agents, or combinations of agents, will result in the most clinically beneficial outcomes for patients. Large-scale trials are still required to determine the effects of the long-term suppression of inflammation on CVDs through the use of RAAS modulating agents, as well as to determine how closely markers of inflammatory activity may correlate with CVD outcomes. **(Am J Cardiol 2006;98:121–128)**

The renin-angiotensin-aldosterone system (RAAS) plays an integral role in the preservation of hemodynamic stability through the regulation of extracellular fluid volume, sodium balance, and cardiac and vascular trophic effects. In addition, overactivity of the RAAS is associated with the development of atherosclerosis, hypertension, left ventricular hypertrophy, and cardiovascular events, such as myocardial infarction, stroke, congestive heart failure, and nephrosclerosis. Angiotensin II, the major effector peptide in the RAAS, is recognized for its facilitative role in the mechanisms underlying cardiovascular and renal diseases. Most of the known pressor, proliferative, and profibrotic actions of angiotensin II are mediated through its binding to the angiotensin type 1 (AT_1) receptor. Figure 1 illustrates the major bioactive components of the RAAS produced from the conversion of angiotensinogen to angiotensin I in the circulation and tissues. The interaction of angiotensin I with angiotensin-converting enzyme (ACE) forms angiotensin II, whereas additional angiotensin peptides, such as angiotensin-(1-7), are generated from either angiotensin I by the action of several tissue endopeptidases or the metabolism of angiotensin II by ACE-2, a newly recognized ACE homologue.[1] Angiotensin II and angiotensin-(1-7) generally have opposing actions in the regulation of cytokines, chemokines, adhesion molecules, and nitric oxide. It is now apparent that the RAAS plays a pivotal role in the initiation and maintenance of the vascular inflammatory response, and inflammation is a key mechanism in the development of atherosclerosis.[2] Neutralization of the actions of angiotensin II by ACE inhibitors and angiotensin receptor blockers (ARBs) exerts antihypertensive and anti-inflammatory effects.[3] Because the anti-inflammatory effects of these classes of drugs may contribute to their efficacy in the treatment and prevention of cardiac and vascular events, these data support a proinflammatory role of angiotensin II in cardiovascular disease (CVDs).

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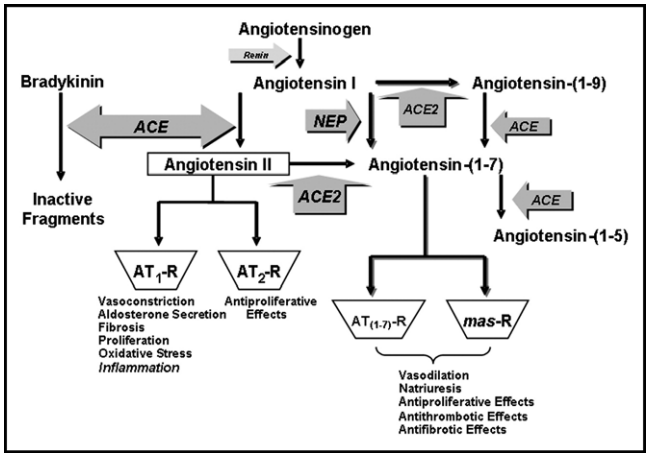

Figure 1. Biochemical mechanisms for the production of angiotensin peptides. Illustrated are the traditional as well as newly recognized enzymatic pathways leading to the formation and metabolism of products derived from angiotensinogen. ACE cleaves angiotensin I to generate angiotensin II (angiotensin-[1-8]), while neutral endopeptidases cleaves angiotensin I to produce angiotensin-(1-7). Studies of the catabolic pathways for angiotensin-(1-7) degradation showed that ACE hydrolyzes the heptapeptide into biologically inactive angiotensin-(1-5), a finding that underscores a contribution of the vasodilatory and antiproliferative actions of angiotensin-(1-7) to the mode of action of ACE inhibitors. ACE-2 is a newly identified enzyme that catalyzes the conversion of angiotensin I to angiotensin-(1-9) and, more important, converts angiotensin II into angiotensin-(1-7). The proinflammatory actions of angiotensin II are mediated primarily through the AT_1 receptor, whereas the anti-inflammatory actions of angiotensin-(1-7) are exerted through receptors that include a mas oncogene-encoded G protein-coupled receptor. AT-R = angiotensin type receptor; mas-R = mas receptor.

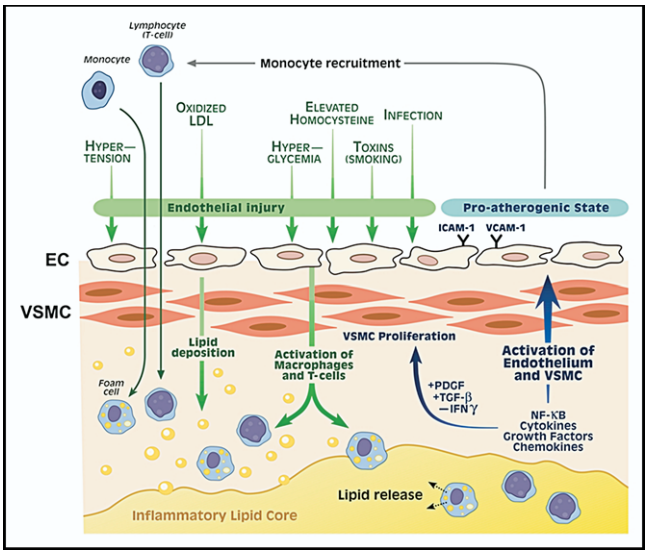

Figure 2. The role of inflammation in atherosclerosis. Endothelial injury stimulates the migration of low-density lipoprotein cholesterol to the intima, wherein the low-density lipoprotein cholesterol undergoes modification. The modified low-density lipoprotein cholesterol initiates a chronic inflammatory response that ultimately leads to the development of atherosclerosis. EC = endothelial cell; IFN-γ = interferon-γ; NF-kβ = nuclear factor-$\kappa\beta$; PDGF = platelet-derived growth factor; TGF-β = transforming growth factor beta. Adapted from Figure 1 in DeGraba et al,[51] with permission.

Inflammation in Atherosclerosis

Atherosclerosis is a chronic, subendothelial, low-grade inflammatory reaction initiated by a host of risk factors. Figure 2 shows atherosclerotic plaque formation occurring in response to injury precipitated by risk factors, such as hypertension, hyperglycemia, cigarette smoking, hyperlipidemia, and/or infections. It is generally conceded that the initial endothelial injury stimulates the insudation of lipids to the site of the injury. Figure 3 further illustrates a series of proatherogenic events originating with low-density lipoprotein cholesterol accumulation in the intima and its oxidative modification. Oxidatively modified low-density lipoprotein cholesterol is believed to initiate an inflammatory response associated with the expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin. Peripheral blood leukocytes are subsequently recruited to the vascular wall by the expression of adhesion molecules and the release of chemokines, such as monocyte chemoattractant protein-1 (MCP-1) by endothelial cells, vascular smooth muscle cells (VSMCs), and macrophages. Monocyte-derived macrophages infiltrate the site of injury and migrate into the intima, where they ingest the modified low-density lipoprotein cholesterol. Macrophage colony–stimulating factor facilitates this process and the maturation of the lipoprotein-containing macrophages into foam cells. Macrophages and T cells attracted to the site of injury release inflammatory mediators, which enhance the chemotactic state of the developing atherosclerotic plaque. T-cell production of tumor necrosis factor-α (TNF-α) and interferon-α activates vascular endothelial cells, VSMCs, and macrophages. Factors promoting VSMC and fibroblast proliferation are also released by T cells and macrophages, leading to the deposition of an interstitial fibrous matrix that forms the fibrous cap that encloses and stabilizes the underlying plaque. The progression of atherosclerosis depends on the continued recruitment of leukocytes for foam-cell development and lesion advancement. The recruitment of inflammatory cells, in conjunction with the oxidation of low-density lipoprotein cholesterol and VSMC proliferation, results in the formation of a complex lesion containing primarily activated T cells and macrophages, intimal fibrous tissue, esterified and free cholesterol, and a collagenous extracellular matrix.

Changes in the inflammatory profile within atherosclerotic arteries predispose patients to subsequent thromboembolic and ischemic events. The release of proinflammatory cytokines, including TNF-α and interleukin (IL)–1β, from macrophages causes the endothelium of the plaque to change from an anticoagulant to a prothrombotic surface. This is characterized by a reductions in tissue plasminogen activator and protein-S and increases in thromboplastin, matrix metalloproteinases, endothelin-1, platelet-activating factor, plasminogen activator inhibitor-1, ICAM-1, VCAM-1, E-selectin, P-selectin, IL-6, IL-8, and MCP-1. Thrombosis of either coronary or cerebral arteries may be caused by plaque