

*Review Article***The impact of RAS in the cardiovascular complications**

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Abstract

The renin-angiotensin system (RAS) is considered to be an important component of the cardiovascular system due to its critical role in the cardiovascular physiology. However, under pathophysiological conditions, the effects of the RAS can intensify to trigger inflammation and structural remodeling, thus promoting cardiac and vascular damage.

Keywords: RAS; atherosclerosis.

Introduction

The renin-angiotensin system (RAS) is considered to be an important component of the cardiovascular system due to its critical role in cardiovascular physiology. However, dysregulation and overexpression of the RAS induces the initiation of vascular damage and the development of atherosclerotic cardiovascular diseases (CVDs). Worldwide, atherosclerotic CVDs remain the leading cause of mortality (Herrington et al., 2016). This brief review focuses on the role of RAS in atherosclerotic CVDs progression. Furthermore, we highlighted the beneficial outcomes of RAS blockage in Atherosclerotic CVDs progression.

Pathogenesis of atherosclerotic CVDs**(Figure 1)**

The initial injury to the endothelium, that resulting from one of the atherosclerotic cardiovascular risk factors as dyslipidemia, smoking, hypertension and diabetes, alters the endothelial cell surface to become more permeable and adhesive over time. The increased permeability of arterial endothelial cells allows migration of low-density lipoprotein cholesterol (LDL-C) into the intima where it under-goes free radical oxidation to be converted into oxidized low-density lipoprotein (oxLDL). The presence of oxLDL initiates an inflammatory response that includes the increased expression of circulating adhesion molecules as vascular cell adhesion molecule-1 (VCAM-1) and intercellular

adhesion molecule-1 (ICAM-1) (Gimbrone and García-Cardeña 2016).

The presence of adhesion molecules with subsequent release of chemokines by macrophages, vascular smooth muscle cells (VSMCs) and endothelial cells results in the migration of peripheral leukocytes to the vascular wall.

Monocytes adhere to the endothelium and infiltrate into the intima where they differentiate into macrophages, which is facilitated by proteins such as macrophage colony-stimulating factor (M-CSF). Then, these macrophages proceed to ingest the oxidized lipids via their scavenger receptors, thereby resulting in their transformation into lipid-dense macrophage foam cells. Interactions between foam cells and T-lymphocytes cause the release of various inflammatory molecules and cytokines as monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6) and IL-4. These inflammatory molecules and cytokines activate vascular endothelial cells, macrophages and VSMCs (Badimon, et al., 2012).

After that, VSMCs proliferate and migrate from the media to the intima and accumulate along with the macrophages. Furthermore, the interactions between T lymphocytes, macrophages and VSMCs stimulate the secretion of additional inflammatory mediators, resulting in a chronic

inflammatory response, thereby leading to the formation of a sub-endothelial atheromatous fibrous plaque with a fibrous cap. The atheromatous fibrous plaque is considered to be the hallmark of atherosclerosis which vary in their contents of lipids, smooth muscle cells, connective tissue matrix, calcium deposits and vessels (Koenig and Khuseyinova, 2007).

Following formation of a stable plaque, plaque destabilization can occur in the presence of one or more cardiovascular risk factors. The vulnerable plaque can then rupture, resulting in platelet aggregation and thrombosis. The mechanisms of plaque destabilization are complex (Badimon, et al., 2012). Initially, macro-phages release pro-inflammatory cyto-kines that precipitate changes in the plaque surface and create a pro-thrombotic state. Furthermore, levels of protein-S and tissue plasminogen are reduced. In addition, the release of lysosomal enzymes as matrix metalloproteinases (MMPs) from macro-

phages and T cells, together with a reduction in collagen synthesis by VSMCs, results in degradation of the plaque's elastin and collagen fibrous cap. Simultaneous neovascularization occurs, resulting in further destabilization of the plaque and, ultimately, rupture (Mason 2011).

Following plaque rupture, activation of the coagulation cascade, fibrin deposition and platelet activation lead to the formation of a localized thrombus, which can cause obstruction of blood flow in the affected artery resulting in arterial occlusion and tissue ischemia (Badimon, et al., 2012). Plaque rupture can be fatal. If the plaque ruptures suddenly in a coronary artery, this can result in acute coronary syndrome (unstable angina, acute myocardial infarction, and/or sudden death). Alternatively, plaque rupture in a carotid artery leads to symptomatic carotid artery disease and increased risk of ischemic stroke (Mason 2011).

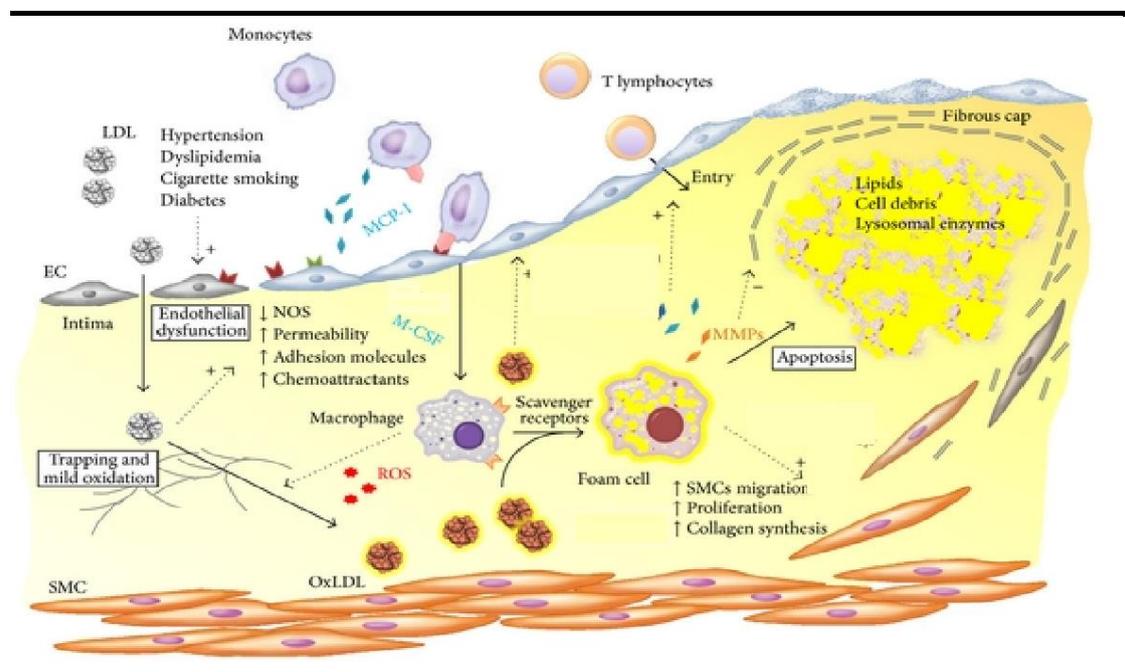


Figure 1. The pathogenesis of atherosclerotic cardiovascular diseases (CVDs)
Quoted from (Maiolino, et al. 2013)

The RAS and atherosclerotic CVDs

progression

The RAS is considered to be an important component of the cardiovascular system due to its critical role in the cardiovascular physiology. However, under pathophysiological conditions, the effects of the RAS can intensify to trigger inflammation and structural remodeling, thus promoting cardiac and vascular damage (Paz Ocaranza, et al., 2020).

Angiotensin II (Ang-II) is the main effector of RAS (Colafella et al., 2019) that is formed from the angiotensin I (Ang-I) cleavage by angiotensin converting enzyme (ACE). Ang-II can bind to Ang-II type 1 receptor (AT1R) or Ang-II type 2 receptor (AT2R). AT1R is primarily responsible for the classic pro-atherogenic effects of Ang-II, whereas the AT2R is reported to present antagonistic effects to the AT1R (Figure 2) (Ding et al., 2016).

Furthermore, Ang-II undergoes the action of angiotensin converting enzyme type 2 (ACE2) to be converted into angiotensin 1–7 (Ang-1-7), which classically interacts with Mas receptor (MasR) producing many anti-atherogenic effects (Figure 2) (Silva, et al., 2020).

Thus, there are two counteract axes of the RAS cascade that include (Ishizuka, et al., 2020):

- (1) Angiotensin converting enzyme, angiotensin II and angiotensin II type 1 receptor (ACE–AngII–AT1R) axis that possess pro-atherogenic effects contributing to increased atherosclerotic CVDs progression.
- (2) Angiotensin converting enzyme 2, angiotensin 1–7 and Mas receptor (ACE2–Ang1–7–MasR) axis that possesses many anti-atherogenic profiles contributing to protection against atherosclerotic cardiovascular events.

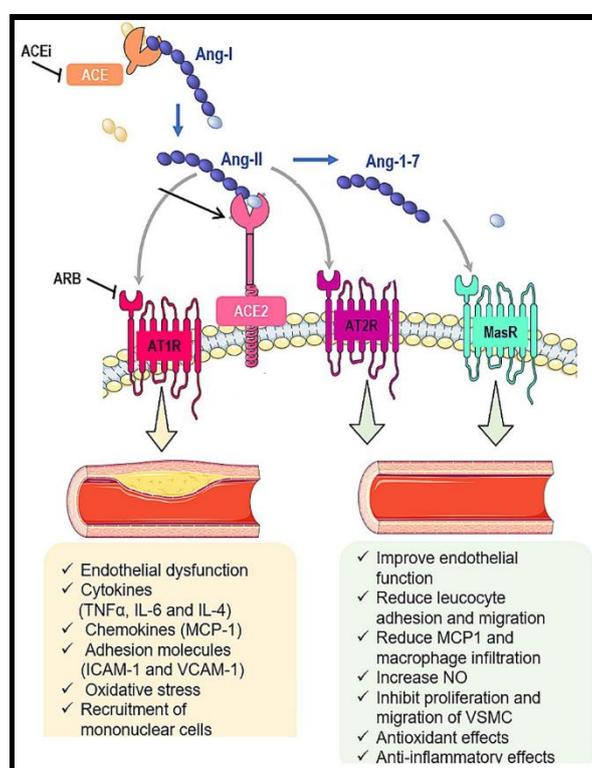


Figure 2. Interactions between the renin-angiotensin system (RAS) and atherosclerosis. Quoted from (Silva, et al., 2020)

The Role of RAS blockage in atherosclerotic CVDs progression

Both ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) block the atherogenic actions of ACE/Ang-II/AT1R pathway either through inhibition of ACE or antagonize binding of Ang-II to AT1R. Thus, pharmacological treatment with ACEIs or ARBs have been shown to interfere in some components of RAS cascade and prevent the atherosclerotic CVDs progression (Silva, et al., 2020).

Conclusion

In conclusion, here we briefly reviewed the role played by RAS components such as Ang-II and Ang-1-7 in atherosclerotic CVDs development. According to what is expected to components of RAS, Ang-II is considered to have pro-atherogenic effects while Ang-1-7 anti-atherogenic profiles. In addition to the direct pressure-related roles of these peptides, their effects on atherosclerotic CVDs involve modulation of endothelial function, oxidative stress, inflammation, cellular migration and proliferation, as well as plaque stability. Pharmacological strategies currently used to modulate the effects of RAS components can offer beneficial outcomes in atherosclerosis.

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