Direct Renin Inhibition
Another Weapon to Modulate the Renin-Angiotensin System in Postinfarction Remodeling?

Stefano Perlini, Francesco Salinaro, Maria Luisa Fonte

The process of cardiac healing and recovery after an acute myocardial infarction encompasses profound changes in the necrotic area (“infarct zone”), in the neighboring ischemic zone (“area at risk”), and in the nonischemic myocardium (“nonischemic region”). Patient’s prognosis ultimately depends on the functional, biochemical, electric, and structural changes taking place in these 3 different areas as a consequence of the acute ischemic event. These extracellular, cellular, and subcellular events are globally referred to as “postinfarction remodeling,” and therapeutic interventions able to slow or reverse its progression have a favorable impact on patient prognosis.1

A pivotal role in these processes is played by the renin-angiotensin-aldosterone system (RAAS) that is undoubtedly hyperactivated after myocardial infarction, together with other neural and endocrine systems. Locally synthesized angiotensin II has been suggested to act as an autocrine, paracrine, and intracrine modulator of cardiac function.2 Notably, the major components of the RAAS components have been shown in cardiac tissue, and extracardiac renin uptake is associated with local release by myocardial mast cells.3

Angiotensin II intracellular signal transduction involves the phosphorylation of several proteins, such as membrane transporters and selective ion channels, structural and contractile proteins, and enzymes that regulate metabolism, protein synthesis, and gene expression. These multiple actions are mediated via complex intracellular signaling pathways, including stimulation of the phospholipase C-inositol 1,4,5-trisphosphate-1,2-diacylglycerol cascade, mitogen-activated protein kinases, tyrosine kinases, RhoA/Rho kinase, and reactive oxygen species generation through vascular NADPH oxidase activation. Beyond directly affecting vasoconstrictor hormones, angiotensin II potentiates the effects of several vasoconstrictor hormones, facilitates the central and peripheral effects of the sympathetic nervous system, stimulates aldosterone production, acts as a local growth factor, enhances protein synthesis and extracellular matrix (ECM) deposition, promotes myocardial production of inflammatory cytokines, and modulates apoptosis/anoikis.2 All of these effects participate in the process of postinfarction remodeling (Figure), and the negative role of RAAS activation in this setting is underscored by the proven efficacy of both angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers4 in attenuating the progression of left ventricular remodeling and in improving prognosis.

However, despite their undisputable beneficial effects, both ACE inhibitors and angiotensin II receptor blockers present some “logical” shortcomings in the attempt to inhibit or at least modulate the RAAS. On the one hand, ACE inhibitors cannot completely block angiotensin II production because of non–ACE-related angiotensin I conversion, are not able to directly interfere with angiotensin receptors, and have several ancillary properties because of another enzymatic effect of ACE, ie, bradykinin degradation. On the other hand, angiotensin II type 1 receptor blockade by angiotensin II receptor blockers is associated with increased concentrations of angiotensin II, possibly acting on different angiotensin receptors and increasing the local concentration of several angiotensin II metabolites with disparate and yet poorly understood actions.5 Another approach is to block the precursor, ie, renin, and, indeed, direct renin inhibition was already targeted 30 years ago to inhibit the RAAS, but low bioavailability and short duration of action of the first-generation renin inhibitors withheld their clinical success. The availability of nonapeptide orally available renin inhibitors is, therefore, a very interesting clinical approach, giving a further opportunity to investigate RAAS physiology in cardiovascular disease. The prototype of this class, aliskiren, is now been tested in various clinical trials, and although some data are already available in the setting of arterial hypertension,4 diabetic nephropathy,5 and heart failure,6 further data are needed to fulfill the promise of this new pharmacological tool.

In the present issue of Hypertension, an interesting piece of information is given by an experimental study on the effects of aliskiren in a mouse model of myocardial infarction.7 In their article, Westermann et al7 showed that subpressor doses of the renin inhibitor have a positive impact on left ventricular systolic and diastolic dysfunction, as well as on cardiac hypertrophy and cardiomyocyte apoptosis. A 10-day treatment with aliskiren after coronary ligation normalized the phosphorylation of mitogen-activated protein kinases extracellular signal-regulated kinase 1/2 and p38, attenuated matrix metalloproteinase 9 upregulation, and increased the

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expression of the matrix metalloproteinase tissue inhibitor 1 in the infarcted area, without affecting collagen content. Taken together, these data indicate that, early after an acute experimental infarction, renin inhibition is able to modulate several functional, structural, biochemical, and intracellular effects of angiotensin II without endangering the process of myocardial scar formation in the infarcted area, at least as far as collagen accumulation is concerned. The latter is very important, especially in the early phases of postinfarction remodeling. In the necrotic area, the removal of cellular debris and the concomitant inflammation are associated with the formation of granulation tissue that further evolves to progressive collagen deposition and maturation. These processes eventually lead to the formation of a stiff fibrous scar that preserves myocardial wall integrity, as well as left ventricular geometry. In the acute setting, preload (ie, chamber dimensions) and rate of pressure development (ie, nonischemic myocardium contractility) are the main determinants of systolic bulging of the ischemic area that is related to the risk of acute rupture and of progressive dyskinesia. In the transition from the acute to the chronic phase, collagen deposition is associated with complex changes in the fine balance between ECM synthesis and degradation, and a specific spatial and temporal profile of matrix metalloproteinase release has been shown to occur after myocardial infarction. At the same time, the nonischemic region undergoes profound structural changes involving cardiomyocyte hypertrophy, fibroblast hyperplasia, and myocardial fibrosis, attributable (among other factors) to the alterations in regional loading conditions caused by the dysfunction of both the infarcted area and the ischemic border zone and to the activation of several local and systemic regulatory systems.

In the setting of postinfarction remodeling, it is important to consider several aspects possibly related to RAAS modulation. Afterload reduction might be desirable in some but not in all patients, and direct effects of any intervention should be dissected from the effects that are related to blood pressure reduction. ECM remodeling has different physiopathological consequences, because an early fibrotic reaction in the infarcted area prevents the risk of further dilation, dyskinesia, and rupture of the ventricular wall, whereas subsequent excessive collagen deposition in the nonischemic remote region increases myocardial and chamber stiffness, thereby worsening diastolic function and enhancing electric nonuniformity. Moreover, matrix metalloproteinases participate not only in the extensive ECM remodeling but also in the inflammatory reaction taking place in both the infarcted and the noninfarcted areas. In their experiment, Westermann et al used subpressor doses of aliskiren to minimize any possible interference of blood pressure. However, renin inhibition blunted the infarction-related changes in some indices of angiotensin II intracellular signaling, in cardiac hypertrophic response, and in cardiomyocyte apoptosis, while improving left ventricular systolic and diastolic dysfunction, chamber dilation, and pulmonary congestion. Unfortunately, no information was given on ECM structure and remodeling, with the notable exception of the observed reduction in the extent of collagen deposition in the infarcted area. Additional experimental and clinical studies are clearly needed to clarify the effects of renin inhibition on ECM remodeling and fibrosis after acute myocardial infarction.

On the whole, these experimental results further raise the expectation surrounding the clinical trials that will eventually define whether aliskiren will become not only a powerful tool to modulate a fundamental physiological system but also a new weapon against cardiovascular diseases.

Disclosures

None.

References

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