Role of RAAS inhibition in preventing left ventricular remodeling in patients post myocardial infarction

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Conflicts of interest: Prof. Marzilli has given lectures on Ischemic Heart Disease for Servier International.

Abstract

Left ventricular remodeling after myocardial infarction has been identified as a predictor of adverse outcome and as a relevant therapeutic target. It has been shown that upregulation of the renin–angiotensin–aldosterone system (RAAS)* has an important role in the pathogenesis of cardiac remodeling. In this paper we summarize evidence on the role of the RAAS in the development of left ventricular remodeling and review major trials based on the addition of an RAAS inhibitor to standard therapy in the post myocardial infarction setting to prevent remodeling and improve outcome.
■ *Heart Metab.* 2010;47:9–13.

Keywords: Aldosterone blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, left ventricular remodeling, renin–angiotensin–aldosterone system

Introduction

Mechanical reperfusion therapy and current pharmacological treatment can, to some extent, limit cardiac dysfunction and adverse ventricular remodeling in patients with acute myocardial infarction; however, progressive ventricular dilatation is still observed in a substantial proportion of patients [1]. Left ventricular remodeling includes changes in ventricular structure, volume, and shape after an acute myocardial infarction. The process develops in two phases: an early one, with expansion limited to the infarct zone, and a late one, the so-called late remodeling phase, when the entire left ventricle undergoes progressive dilatation. Left ventricular remodeling eventually results in chamber dilatation and sphericity [2]. Initially, ventricular dilatation may be useful in maintaining an adequate cardiac output despite the loss of contractile elements; however, at the same time, it is a detrimental process because it renders the ventricle more prone to dysfunction and eventually to heart failure. Importantly, left ventricular remodeling may also be associated with an increased risk of ventricular arrhythmias.

Left ventricular remodeling is most pronounced in patients with a large anterior infarction or microvascular dysfunction, or both. Endocrine/autocrine/paracrine neurohormonal signaling is the driver for the process, the acute phase of myocardial infarction being characterized by a short-lived but intense neuroendocrine activation, with plasma concentrations of angiotensin II peaking at 3 days. Myocyte hypertrophy and excess extracellular deposition of collagen are key histologic components.

Activation of the renin–angiotensin–aldosterone system (RAAS) participates actively in the process of left ventricular remodeling. Renin is a proteolytic enzyme that is released into the circulation primarily by the juxtaglomerular cells. Its release is stimulated by renal artery hypotension and is followed by sympathetic nerve activation and by decreased delivery of sodium to the distal renal tubules. When renin is released into the blood, it acts upon a circulating substrate, angiotensinogen, that undergoes a proteolytic cleavage to form the decapeptide, angiotensin I. Vascular endothelium, particularly in the lungs, has an enzyme, angiotensin converting enzyme (ACE), that cleaves off two amino acids to form the active octapeptide, angiotensin II.

Under pathological conditions, the RAAS is activated by several factors – in particular, inflammation and endothelial dysfunction. Its stimulation, with the spillover of aldosterone, is responsible for extracellular matrix proliferation and contributes to the increased deposition of fibrous tissue within the ventricular myocardium [3]. The presence of myocardial fibrosis and endothelial dysfunction may affect the coronary microcirculation; in particular, the decrease in myocardial capillary density can contribute to the progression of left ventricular remodeling towards heart failure [4]. For this and other reasons, therapeutic interventions in patients with post infarction left ventricular dysfunction should be aimed at preventing the activation of the RAAS, with possible beneficial effects on left ventricular structure, size, and function. In this respect, a number of pharmacological approaches have demonstrated their efficacy and have significantly reduced mortality and morbidity in patients with a history of acute myocardial infarction.

Inhibition of the renin–angiotensin–aldosterone system

ACE inhibitors were the first drugs to be used to block the RAAS. Inhibition of ACE results in a decrease in the concentration of angiotensin II at the angiotensin receptor sites. Over the past 25 years, several clinical trials have demonstrated the beneficial effects of ACE inhibitors in patients with acute myocardial infarction, with favorable prognostic implications.

The Survival And Ventricular Enlargement (SAVE) trial was a landmark study by Pfeiffer et al [5]. They enrolled patients with left ventricular dysfunction (ejection fraction no greater than 40%) after acute myocardial infarction, who were treated with captopril, starting between 3 and 16 days after admission to hospital. An attenuation of ventricular enlargement became apparent after 12 months and was associated with a significant reduction in morbidity and mortality. In the Studies Of Left Ventricular Dysfunction Treatment and Prevention (SOLVD) trial [6], patients with acute myocardial infarction, ejection fraction <35%, with or without signs and symptoms of heart failure, were allocated randomly to groups receive to enalapril or placebo within the 24–36 hours from their admission to hospital. The study again showed an improved survival in patients receiving the ACE inhibitor. An echocardiographic substudy of the SOLVD trial demonstrated a trend toward reduction in left ventricular end-diastolic volume in the enalapril group with respect to those receiving placebo [7] (*Figure 1*). In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) trial, administration of lisinopril was associated with an improved outcome in patients treated after 24–36 hours from an acute myocardial infarction. The beneficial effects of the drug on left ventricular volumes have been documented in an echocardiography substudy [8] of the main trial. A significant reduction in left ventricular enlargement was already present after 6 weeks of lisinopril treatment. According to the study investigators, early RAAS blockade should be included in a systematic strategy of prevention of post infarction left ventricular remodeling.

Most of the above-mentioned trials did not include elderly patients. As aging is a factor well known to be involved in the process of left ventricular remodeling, a study was designed to investigate the effects of a relatively new ACE inhibitor, perindopril, in elderly patients diagnosed with acute myocardial infarction. In the Perindopril and Remodeling in Elderly With Acute Myocardial Infarction (PREAMI) trial, 1252 post myocardial infarction patients aged at least 65 years with ejection fractions of at least 40% were allocated randomly to groups to receive perindopril or placebo. The study showed that the administration of perindopril was associated with a 0.22 absolute risk reduction in the composite endpoint of death, admission to hospital because of heart failure, or remodeling (95% confidence intervals [CI], 0.16 to 0.28; $P < 0.001$) [9]. In a recent echocardiographic substudy of that trial, it became apparent that the administration of a daily dose of 8 mg of perindopril was associated with prevention of progressive left ventricular dilatation [10].

The selective blockade of the angiotensin II receptor type 1 is another means by which to inhibit the RAAS that is associated with favorable effects on left ventricular structure and function. This is likely to be one of the mechanisms that contribute to the improved outcome of patients with heart failure secondary to postischemic left ventricular dysfunction, as shown by several clinical trials (eg, Candesartan in Heart failure – Assessment of Reduction in Mortality and Morbidity [CHARM] [11], Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist

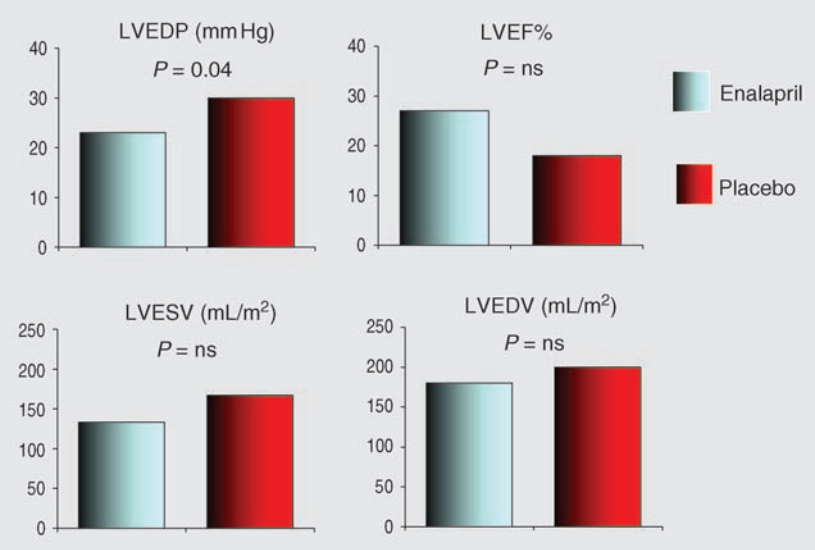

Figure 1. Findings in a substudy of the Studies Of Left Ventricular Dysfunction (SOLVD) trial. LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic pressure; ns, nonsignificant.

Losartan [OPTIMAAL] [12], Valsartan Heart Failure Trial [Val-HeFT] [13]). A positive impact on remodeling has also been observed in patients treated with aldosterone antagonists [14]. Aldosterone exerts several actions that may contribute to adverse left ventricular remodeling: worsening tissue injury, myocyte loss, and reparative myocardial fibrosis. Additional mechanisms include myocyte apoptosis and direct stimulation of collagen synthesis, which may derive from repetitive stunning and oxidative stress. Two large trials evaluated the use of aldosterone receptor antagonists: the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and the Randomized Aldactone Evaluation Study (RALES). The EPHESUS trial compared placebo with the selective aldosterone blockade, eplerenone, added to a background ACE inhibitor – and, in most cases, β-blocker treatment – in patients with post ischemic left ventricular systolic dysfunction. Eplerenone significantly reduced mortality (by 15%), supporting the strategy of adding an aldosterone receptor blocker to an ACE inhibitor or an angiotensin II type 1 receptor blocking agent (ARB). This makes sense from a pathophysiological standpoint, because aldosterone is regulated independently of angiotensin II. Aldosterone blockade is therefore a complementary, rather than a competing, treatment for the survivors of acute myocardial infarction [15]. The RALES trial, which was discontinued early because an interim analysis determined that spironolactone was efficacious by substantially reducing the risk of both mortality and morbidity, confirmed the efficacy of this strategy.

Therapeutic perspectives

Although ACE inhibitors and ARBs have both been shown to be effective in improving mortality and morbidity in acute myocardial infarction complicated by left ventricular systolic dysfunction, left ventricular remodeling remains a frequent and adverse consequence of myocardial infarction. Left ventricular remodeling contributes to the progression from left ventricular dysfunction to heart failure, and markedly affects clinical outcome and quality of life of patients who have suffered myocardial infarction. For this reason, alternative therapeutic options that may be implemented in these patients are actively sought (*Table I*).

A number of new therapeutic interventions targeting left ventricular remodeling have been proposed. Because aldosterone stimulation is recognized to have a negative effect on left ventricular remodeling [16], Chan et al [17] undertook a magnetic resonance imaging study to investigate the addition of spironolactone to candesartan (an angiotensin type II receptor blocker) in patients who had suffered acute myocardial infarction. They reported a significant reduction in left ventricular end-diastolic and end-systolic volumes and an improvement in left ventricular ejection fraction.

Aliskiren, a direct renin antagonist, improved left ventricular function and prevented cardiac remodeling in experimental mice submitted to an acute ischemic injury [18].

After myocardial infarction, excessive deposition of extracellular collagen matrix (ECCM) has been

Table I. Potential therapeutic strategies to prevent left ventricular remodeling.

Nitric oxide modulators/enhancers
Statins
Phosphodiesterase 5A inhibitors
Antioxidants
Metalloproteinase inhibitors
Proangiogenic factors
Antagomirs (micro-RNA* controlling growth promoting factors)
Modulators of proinflammatory cytokines

associated with evidence of left ventricular diastolic dysfunction. Modulation of collagen formation and degradation and control of extracellular matrix deposition have been proposed as possible therapeutic approaches. Preservation of a correct balance between matrix metalloproteinase activity and endogenous tissue inhibitors of matrix metalloproteinases could be an effective therapeutic strategy with which to prevent ventricular remodeling [19].

Collagen formation occurs by eight enzymatic steps: intracellular synthesis of pro-chains, hydroxylation, glycosylation, formation of procollagen triple helixes, secretion into the extracellular space, conversion into less soluble molecules, assembly into fibrils, and aggregation into fibers. Prolyl-4-hydroxylase catalyzes the hydroxylation of proline on α monomers to yield stable protocollagen molecules that are secreted into the ECCM; this enzyme could be a possible therapeutic target. Both ACE inhibitors and ARBs, in addition to aldosterone blockers, decrease ECCM. The aldosterone antagonist, spironolactone, decreases collagen turnover and ARBs also decrease prolyl-4-hydroxylase [20–23]. Protecting the ECCM post myocardial infarction could be a promising target for treatment.

A new pharmacological option may be offered by agents that inhibit both the ACE and neutral endopeptidase enzymes: vasopeptidase inhibitors (*Figure 2*). Lapointe et al [24] demonstrated that the neutral endopeptidase inhibitor, omapatrilat, improved post myocardial infarction cardiac function and prevented cardiac remodeling in a rat model.

However, not all treatments that were associated with a beneficial effect on left ventricular remodeling

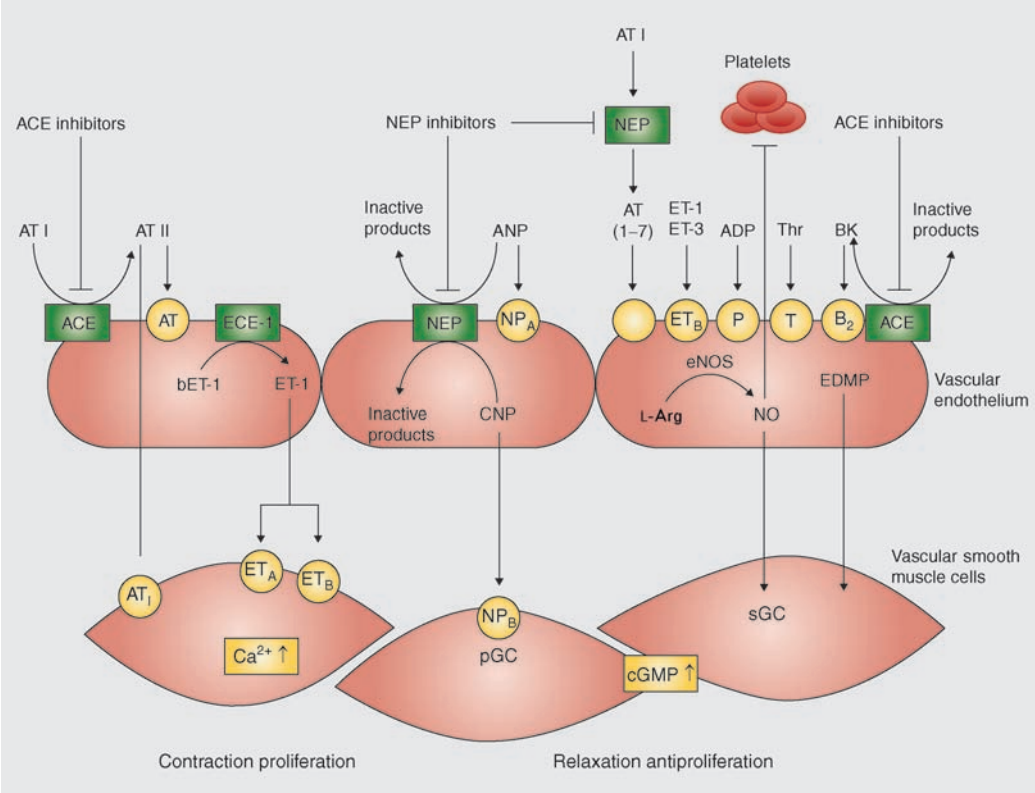

Figure 2. Mechanism of action of vasopeptidase inhibitors. Synergistic effects resulting from combined inhibition of angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP) are due to similar mechanisms — blockade of angiotensin (AT) synthesis and concomitant potentiation of natriuretic peptides and bradykinin* (BK), leading to vasodilatation, natriuresis and improvement in myocardial function. ↑, increased; ANP, atrial natriuretic peptide; AT I, angiotensin I; AT II, angiotensin II; AT (1–7), angiotensin II types 1–7 receptors; B_2, bradykinin receptor; bET-1, big endothelin-1; cGMP, cyclic guanosine 3′5′-monophosphate; CNP, C-type natriuretic peptide; ECE-1, endothelin converting enzyme-1; EDMP, endothelial cell-derived microparticules; eNOS, endothelial nitric oxide synthase; ET-1, ET-3, endothelins 1 and 3; ET_A, ET_B, endothelins A and B receptors; L-Arg, L-arginine; NO, nitric oxide; NP_A, NP_B, natriuretic peptide receptors A and B; P, adenosine receptor; pGC, particular guanylyl cyclase; sGC, soluble guanylyl cyclase; T, thrombin receptor; Thr, thrombin.*

have later been associated with an improved clinical outcome, suggesting that disease progression may also occur through alternative mechanisms, independent of cardiac remodeling [25]. It is possible that sex differences could have a critical role in this respect, based on different concentrations of the sex-related hormones, estrogens and testosterone [26].

Summary

RAAS inhibition in the setting of acute myocardial infarction represents an established strategy to reduce cardiovascular mortality and morbidity. The beneficial effects of RAAS inhibition with ACE inhibitors, ARBs, and aldosterone antagonists can be attributed, at least in part, to the prevention or attenuation of left ventricular remodeling.

* see glossary for definition of these terms. ■

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