CARDIAC REMODELING AND RENIN-ANGIOTENSIN SYSTEM.

Germán E. González, Nidia Basso, Ricardo J. Gelpi, Celina Morales.

Institute of Cardiovascular Physiopathology, Department of Pathology, School of Medicine, University of Buenos Aires. E-mail: mmorales@fmed.uba.ar

SUMMARY.

Myocardial infarction (MI) leads to structural alterations involving the infarcted as well as the non-infarcted areas in a process known as ventricular remodeling. The early phase of remodeling, which starts at the beginning of the MI, is associated with geometric changes and dilation of the infarct zone, as a process collectively known as expansion of the scar. Subsequently, this dilation may progress to the whole ventricle and it is associated with myocytes hypertrophy and fibrosis in the remote zones. These structural changes start on during the initial phase of the healing process of the infarction, contribute to ventricular dysfunction, cause a progression to heart failure and increase mortality. The systemic and cardiac renin-angiotensin systems (RAS) are stimulated post-MI and actively participate in ventricular remodeling, favoring the healing process of the infarct area as well as myocytes hypertrophy, fibrosis, and most of the events associated to the remodeling of non-MI zones. In this review, we analyze different general aspects of postmyocardial infarct ventricular remodeling and the activation and participation of the renin- angiotensin system in its evolution.

INTRODUCTION.

Ventricular remodeling (VR) represents the anatomopathological and physiopathological basis of ventricular dysfunction in heart failure. It is interesting to consider the contribution of local and systemic hormonal systems in the evolution of the morphological changes that are associated in particular to post-myocardial infarction VR. This review analyzes some general aspects of post-infarction VR and how its evolution is linked to the activation and participation of the renin-angiotensin system (RAS).

VENTRICULAR REMODELING.

VR is defined as "an adaptation of the heart chambers to adjust their size and shape in response to long-term alterations in the hemodynamic conditions of ventricular load..." This change in ventricular geometry involves structural alterations of heart mass and shape[1], and is directly correlated to mortality[2].
VR and heart failure are the common endpoint in most primary cardiovascular diseases. Therefore, to consider remodeling only as a change in ventricular geometry would limit us to a very small part of a highly complex process.

RENIN-ANGIOTENSIN SYSTEM IN VENTRICULAR REMODELING.

The RAS has classically been considered as an endocrine system linked to the regulation of blood pressure and plasma volume, with the octapeptide angiotensin II (Ang II) being its main physiological mediator. Nevertheless it is now known that the RAS is wholly involved in cardiovascular homeostasis, both in healthy organisms and in most physiopathological cardiovascular disorders linked to VR

ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN MYOCARDIAL INFARCTION.

Sun et al.[3] showed in rats with experimental myocardial infarction, that there is an increase in the expression and activation of the angiotensin-converting enzyme (ACE) and the density of Ang II type 1 receptors (AT1) from the beginning of infarction, at both the infarct zone and remote zones. Nevertheless, how early the RAS activation occurs may differ according to the species considered. Recent studies at our laboratory revealed that in rabbit hearts with permanent coronary artery ligation, the expression of AT1 receptors increased at 15 and 35 days, both at the infarct zone and at remote zones. On the contrary, levels of Ang II augmented between 3 hours and 4 days post-MI in non-infarcted myocardium, and as from 4 days at the infarct zone.

This evidence could have important implications regarding the therapeutic window to use RAS blockers or ACE inhibitors in myocardial infarction. In this regard, noticeably, it has been confirmed that each component of the RAS regulates different stages of the repair process[4] after infarction. It has been demonstrated that the ACE is activated early at the infarct zone, increasing local levels of Ang II that participates actively in the process of tissue repair at the necrotic zone. At the same time it was found that Ang II can be produced by the macrophages and myofibroblasts present at the infarct site and would contribute autocrinely and paracrinely during the repair process of the infarct zone. In this regard, it would also stimulate oxidative stress, starting the inflammatory response and the synthesis of transforming growth factor β (TGFβ), thus, promoting reparative fibrosis.

Simultaneously with the increase in collagen synthesis, both at the infarct zone and at remote zones, its degradation starts up through the activation of matrix metalloproteinases (MMP)[5]. Recent evidence shows that ACE inhibitors, AT1 receptor blockers and β blockers are associated to changes in the MMP/TIMP balance, which may alter the distensibility of the myocardial wall[6] (Table 1).

Table 1. *Effect of different classes of drugs that block the renin-angiotensin system on the activity of matrix metalloproteinases and their inhibitors (TIMP) (adapted from Vanhoutte, et al. Cardiovasc Res. 2006; 69: 604-613)*

Treatment		Animal model	Effects on MMP/IMMP vs. untreated
Drug	Example		
ACEI	Ramipril	MI in rats	MMP-2 ↓/ MMP-4 ↑
	Trandolapril	MI in rats	MMP-2 ↓
ARB	Valsartan	I-R in dogs	TIMP-3 ↑
	Losartan	C.C. in hamster	MMP-1, 2, 9; TIMP-1 ↓

ACEI: converting enzyme inhibitors, ARB: angiotensin II AT1 receptor blockers, CC: congestive cardiopathy. I-R: ischemia and reperfusion.

The progressive deposition of collagen that occurs during this stage gives rise to more organized areas of fibrosis, which will eventually form the scar that will replace the necrotic zone.

PHYSIOPATHOLOGICAL AND MORPHOLOGICAL ASPECTS OF POST-INFARCTION VENTRICULAR REMODELING

When myocardial infarction is considered to be the triggering factor of VR, the new morphology that the ventricle will adopt and, in principle, will enable it to adapt to the hemodynamic changes caused by the loss of myocytes, depends on the shape and size of the lesion[7], as well as on the inflammatory response involved in the reparative process. Global morphological changes are also a consequence of the reaction of zones remote from the infarct, in response to the interrelation of factors involving the reparative process of the infarct zone, intra-ventricular hemodynamic changes and both local and systemic neurohormonal activation. Throughout this process the RAS plays a major role.

The decrease in the ejection fraction caused by the infarction increases the volume at the end of the systole and produces ventricular dilation. This dilation results from the extent of necrotic myocytes and the capacity of the non-infarcted muscle to respond to the intraventricular hemodynamic changes produced by the infarction. The speed of the healing process and the increased wall stress in the infarct zone influence its morphological changes, an acute "dilation" and thinning of the necrotic zone occur at the beginning of the infarction, which could lead to a process known as infarct expansion. Thus, restructuring of the necrotic zone is considered to be one of the first morphological manifestations characterizing VR.

REMODELING OF INFARCT REMOTE ZONES. THE RAS PARTICIPATION.

The main histopathological changes observed in the remote zone are characterized by myocyte hypertrophy[8] and fibroblast hyperplasia[9]. These morphological changes are accompanied by an increase in collagen deposit in the interstitium, a process known as "reactive" fibrosis distant from the infarct zone[9].

The loss of contractile mass demands that the non-infarcted myocardium maintain the pumping function, while the reparative process of the infarct zone is underway. Thus, the consequent hemodynamic overload with loss of myocytes starts up a set of morphological and functional changes in the non-ischemic myocardium, which will characterize an advanced stage of VR. Therefore, during this stage of the VR process there will be morphological changes in the non-infarcted zones and although they began to develop in the early stages of infarction, they appear late in this process. Thus, while myocytes hypertrophy and changes in ventricular architecture would enable redistribution of wall stress in the infarct zone, the progressive increase in fibrosis stabilizes the distension forces, preventing its deformation[10].

The capacity of the heart to adjust its mass to different load conditions is an essential feature during the remodeling process, which is achieved through myocytes developing hypertrophy[1]. In addition, there will be remodeling of all the components of the extracellular matrix[6].

Different physiological and pathological heart situations that continuously increase ventricular load conditions may result in stimuli that can generate myocytes hypertrophy. In this case, the hypertrophy is part of an adaptive, compensatory response to the increase in ventricular load conditions, attenuating the increase in wall stress produced by progressive

ventricular dilation. Rubin et al.[11] confirmed in rats, after 5-weeks of myocardial infarction, that the degree of compensatory hypertrophy, the non-infarcted myocardial area and the diameter of the myocytes of the non-infarcted wall are directly related to the infarct size. Nevertheless, myocardial growth capacity seems to be limited, since the degree of compensatory hypertrophy developed by myocytes of the non-infarcted zone was similar when infarction size was between 15 to 30%, and when it was greater than 30%. This limitation of cell growth might regulate the functional response[12].

Anversa et al.[13] demonstrated in rats that 3 days after coronary ligation, the volume of viable myocardium and the volume of myocytes increase proportionately. Moreover, they linked the increase in the expression of all the RAS components, particularly Ang II, to the development of compensatory hypertrophy[14]. Myocyte hypertrophy, like extracellular matrix remodeling, is regulated by mechanical factors, such as stretching, and by neurohormonal factors. The latter adjust fetal gene expression and cell growth through the activation of cell surface receptors or intracellular non-receptor pathways[15].

A variety of hormonal agents, such as endothelin, Ang II, insulin-like growth factor (IGF-I), TGFβ and fibroblast growth factor, whose expression increases after infarction, regulate both the synthesis of structural proteins and the expression of ANP and BNP. Moreover, in rats, an increase in the expression of the IGF-I has been found in viable myocytes adjacent to the infarction[16].

The local increase of Ang II, mediated by the myocyte stretching and through the activation of the AT1 receptor, is another important stimulus for the initiation of myocytes and cells of the extracellular matrix hypertrophy. Sadoshima et al.[17] observed an increase in Ang II within cytoplasmic granules 30 minutes after mechanical stretching of the myocardium. This increase in protein synthesis in the myocytes was blocked by an AT1 receptor antagonist[18]. Different authors have studied the effect of the RAS inhibiting drugs on the proliferation of non-myocyte cells and the deposition of collagen after myocardial infarction[8]. Thus, it has been observed that ACE inhibitors as well as AT1 blockers, reduced non-myocyte cell proliferation to levels comparable to those in sham animals. Similar results were observed for collagen deposition.

Recent studies at our laboratory proved that at 4 days post-infarction in rabbits, AT1 receptors blockade reduced the proliferation of perivascular fibroblasts and the interstitial and endocardial fibrosis in septum and right ventricle[19].

On the other hand, most cytokines that increase their expression in the infarct zone, such as interleukins, tumor necrosis factor, and TGFβ, are also expressed in non-infarcted zones[20]. These cytokines activate the hypertrophy mechanisms of myocytes proceeding in an autocrine or paracrine form.

ROLE OF INHIBITORS OF THE RENIN ANGIOTENSIN SYSTEM IN POST-INFARCTION VENTRICULAR REMODELING.

The fact that the RAS is activated as from very early stages and throughout the evolution of the infarction means that it fulfills essential functions during this period and in the entire VR process[4].

Today, drugs such as ACE inhibitors are used regularly in the treatment of patients with congestive cardiac failure; nevertheless, the action of AT1 blockers is still under discussion. Due to the major participation of RAS in the morphological and functional changes associated with post-infarction VR, and based on experimental studies by Pfeffer and Braunwald[21], inhibitors of the RAS began to be used frequently in clinical practice to modify the evolution of VR.
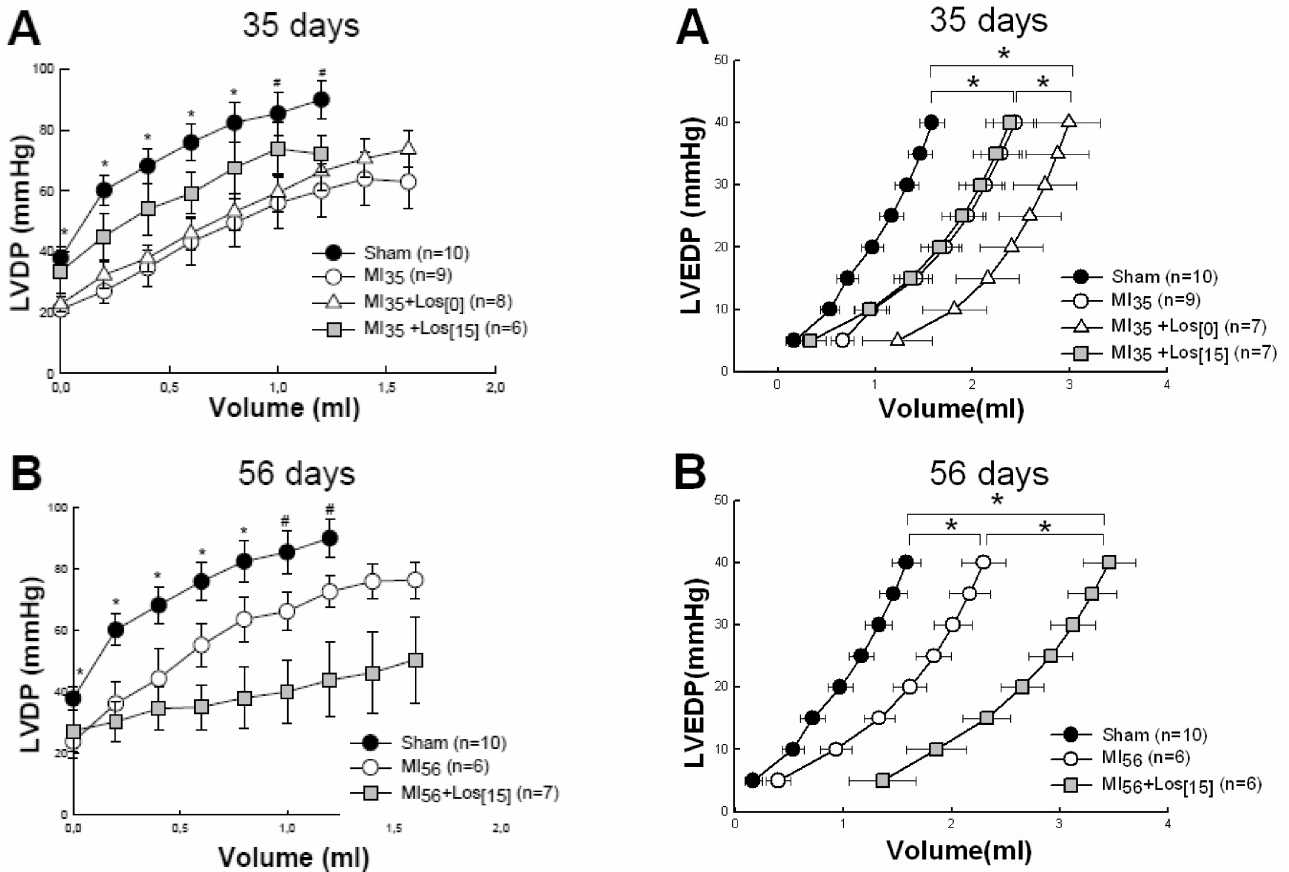
Figure 1: *Systolic (left) and diastolic (right) pressure-volume curves[19]. *p<0.05 vs MI and MI+Los[15]; #p<0.05 vs MI.*

There is great interest in cardiological practice on the study of morphological and functional changes in the heart once the ischemic process sets in, and their modification by drugs that modulate the cardiac RAS. The experimental evaluation of these drugs in myocardial infarction has provided better understanding of the mechanisms that are activated during infarction and that participate on changes in ventricular geometry. In this sense, it has been demonstrated that ACE inhibitors and AT1 receptor blockers reduce mortality and beneficially modify VR by operating not only on cardiac myocytes[22], but also on each of the components of the extracellular matrix[23]. Several experimental studies have found that these drugs reduce the degree of fibrosis in the infarct and remote zones[8; 23]. However, the involved mechanisms are a matter of controversy and require further research.

Schieffer et al.[24] described, in rats with experimental myocardial infarction, that enalapril and losartan treatment induced a reduction in compensatory hypertrophy and attenuation of interstitial fibrosis in remote zones of the left ventricle.

Thai et al.[25] recently confirmed that the reduction of fibrosis in experimental myocardial infarction is accompanied by an attenuation of ventricular stiffness in the remote zone after losartan administration. Nevertheless, other studies on different myocardial infarction models that evaluated the effect of AT1 receptor blockade on VR are contradictory, and there is no real agreement on the possible beneficial effect of these drugs on VR[8; 26; 27]. Therefore, the effect of these drugs on post-infarction remodeling should be taken cautiously and the ultimate benefit they may have on each of its features should be considered. Using rats as an experimental model of infarction, several authors have
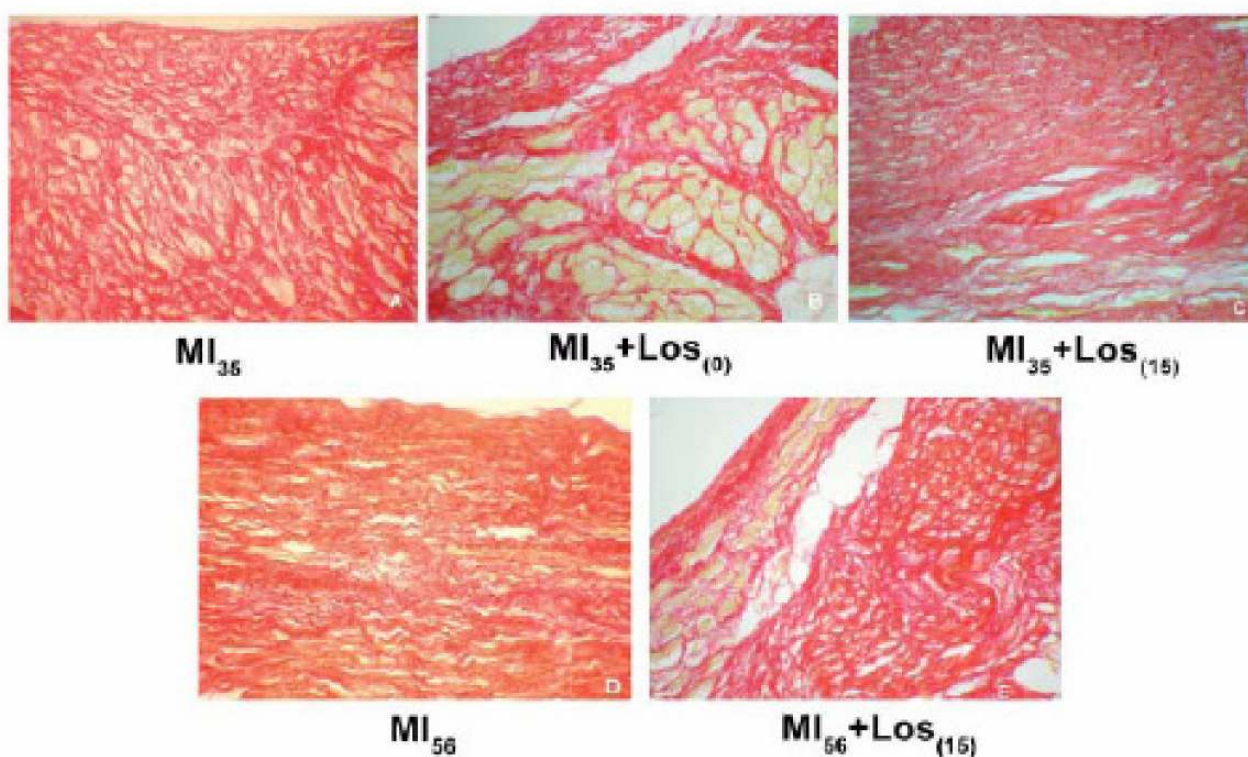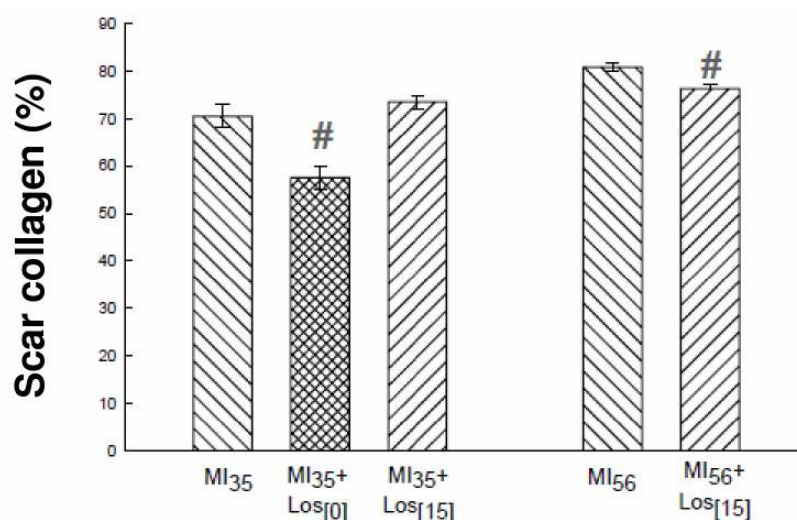
Figure 2: *Scars collagen concentration in animals treated at different times of infarction evolution. Bottom: microphotographs, corresponding to the groups in the figure, showing the scar zone in sections stained using the picrosirius red technique[19]. # p< 0.05 vs MI.*

independently described that captopril and/or losartan administration attenuate hypertrophy[24; 25] and reduce ventricular dilation[21; 27] and fibrosis[25; 28] at both the infarct and remote zones. However, following quinapril and losartan administration to rats during 6 months after experimental infarction, Hu et al.[29], were unable to prevent the ventricular dilation. Xia et al.[30] have recently suggested that the administration of fonsartan 3 and 24 hours post-infarction would reduce infarction size and improve the systolic and diastolic dysfunction of cardiac failure, although they were not able to show a reduction in the ventricular cavity diameter. Chronic AT1 receptor blockade could also have an unfavorable effect on post-infarction remodeling[19]. Indeed, in experimental studies on rabbits with myocardial infarction,
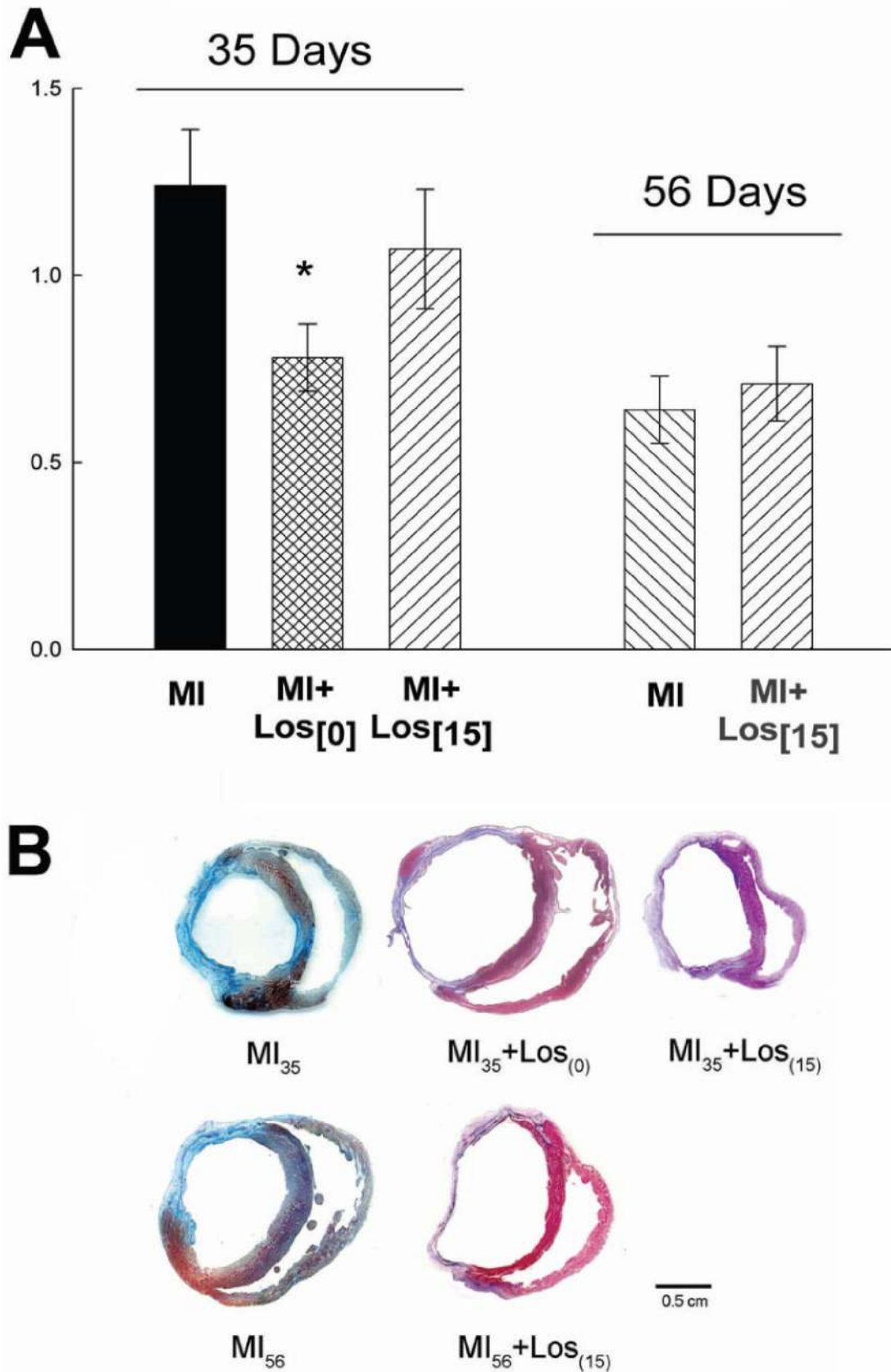
Figure 3: *Scar thinning calculated as the ratio between the thickness of the scar and the average thickness of non-infarcted septum in the same slice. This was measured at different times of infarction evolution. Bottom: histological sections, stained using Masson's Trichromic technique, for the different groups in the figure. Note the thinner scar and the size of the ventricular cavity in chronically treated animals[19]. * p<0,05 vs MI.*

we evaluated the effect on VR according to different initiation and duration times of losartan treatment[19]. The results of these studies indicate that losartan administration could also generate an unfavorable effect on VR, depending on the duration of the treatment and not on the initiation period. This unfavorable effect would be due to the increase in ventricular dilation and the decline in contractility observed in chronically treated animals (Figure 1). Similarly, we found a reduction of collagen (Figure 2) and a thinning of the scar (Figure 3). Nevertheless, when losartan was administered for 20 days, the decline in contractility was attenuated and no increase in ventricular dilation was observed[19]. These results reveal the importance of finding an adequate therapeutic window to begin AT1 blockers treatment. To conclude, exhaustive knowledge of the physiopathology of VR and the participation of each component of the RAS on its evolution would enable the best use of the beneficial therapeutic effects of drugs that block the RAS on many aspects of VR. As mentioned above, there is an apparent dissociation between clinical studies, which show mainly beneficial effects, and experimental studies, which consider more variables and therefore analyze remodeling in greater detail, showing contradictions concerning the final effects of RAS inhibitors

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