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Original Article

Early administration of Enalapril prevents diastolic dysfunction and ventricular remodeling in rabbits with myocardial infarction

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ABSTRACT

We aimed to investigate the role of early administration of Enalapril (Enal) on post-myocardial infarction (MI) ventricular remodeling and diastolic dysfunction in rabbits. White New Zealand rabbits that underwent coronary artery ligature or Sham were divided in three experimental groups: (1) Sham, (2) MI, and (3) MI + Enal. Enal was given by gavage at a dose of 10 mg/kg/day starting at 3 h after surgery for 35 days. At the end of the protocol, we measured (1) mean arterial pressure, (2) left ventricular (LV) + dP/dt_{max}, (3) LV end-diastolic pressure (LVEDP) and isovolumic relaxation (Tau), (4) LV dimensions, (5) LV ejection and shortening fraction, (6) infarct size (Masson's trichrome-stained slices), (7) fibrosis in the infarct and remote zone (Picrosirius red-stained slices), and (8) myocyte cross-sectional area (MCSA) in WGA-stained section. Enal reduced the mean arterial pressure by 30% as compared with untreated animals and Sham ($P<.05$). MI reduced LV + dP/dt_{max} and LV − dP/dt_{max} (mmHg/s), increased LVEDP (mmHg), Tau (ms), and t_{50} (ms) values, suggesting a decrease in the relaxation rate. LV end-diastolic dimension and LV end-systolic dimension (LVESD, mm) increased in untreated MI ($P<.05$ vs. Sham). In contrast, Enal markedly prevented post-MI diastolic dysfunction by significantly decrease LVEDP from 8.2 ± 0.2 to 5.1 ± 0.3 mmHg, Tau from 19.8 ± 0.8 to 15.3 ± 0.9 ms, and t_{50} from 12.4 ± 0.5 to 9.6 ± 0.8 ms as well as reduced LVESD from 15 ± 1.1 to 12 ± 0.8 mm ($P<.05$ MI vs. MI + Enal). Collagen concentration in the scar was unaffected, but chronic treatment with Enal prevented myocardial fibrosis and MCSA in the remote zone. In summary, chronic early administration of Enal to rabbits with experimental MI has a favorable effect on ventricular remodeling and diastolic function by reducing MCSA and fibrosis, without affecting the wound healing.

1 Introduction

After myocardial infarction (MI), a healing process initiates and the heart begins a remodeling process leading to dysfunction and failure. Therefore, an early therapeutic intervention after an infarction remains the cornerstone for the treatment of this pathology since it can revert its unfavorable evolution. It is also widely accepted that early activation of the renin-angiotensin system (RAS) through its main effector, angiotensin II (Ang II), contributes in the development of adverse remodeling and failure [1,2], also promoting the healing process as a physiological mechanism for replacement of necrotic cells by a scar. The use of Ang II blockers or angiotensin conversion enzyme inhibitors has been widely used to prevent adverse remodeling and the development of heart failure [3,4]. Although it is recommended to initiate treatment with angiotensin converting enzyme (ACE) inhibitors from the onset of MI, the role of these drugs to prevent adverse remodeling and diastolic dysfunction is still under discussion [5,6]. Furthermore, it should be considered that the cardiac expression of the RAS components varies depending on the species and can modify the response to these drugs. Clinical and experimental studies have demonstrated that ACE inhibitors improved ventricular remodeling and survival after an MI [7–9], but it is not clear if this beneficial effect includes an improvement of diastolic dysfunction. We have previously showed that the expression of the RAS components in rabbits with MI differs from those described for other species and that chronic treatment with Losartan adversely modified left ventricular (LV) remodeling in hearts with MI [10]. Accordingly, it would be of clinical interest to know whether the early administration

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of ACE inhibitors, whose mechanism of action differs AT1 blockers, in the same experimental conditions modifies differently post-MI remodeling and function. Therefore, the goal was to study the effects of early administration of ACE inhibitors on remodeling and ventricular diastolic function in rabbits with MI.

2 Methods

2.1 Experimental model of MI

White New Zealand rabbits (body weight: 2.0–2.3 kg) were anesthetized with a ketamine (75 mg/kg) and xylazine (0.75 mg/kg), then intubated and mechanically ventilated using a Harvard ventilator (tidal volume: 25 ml) at a respiratory frequency of 34–38 cycles/min, as was previously described [10]. Subsequently, a lateral left thoracotomy followed by a pericardectomy and ligature of a lateral branch of the left coronary artery using a 6.0 silk thread were performed. Finally, the chest was closed in layers, and the animals were allowed to recover from the anesthesia in a quiet environment. Sham-operated animals underwent the same procedure without ligature of the coronary artery. After the animals recovered from the anesthesia, they were housed in individual cages until the end of the protocol. All experiments were approved by the Animal Care and Research Committee of the University of Buenos Aires, and this investigation conforms to the guidelines from the American Physiological Society "Guiding Principles in the Care and Use of Laboratory Animals."

2.2 Protocols and experimental groups

Three experimental groups were performed ($n = 5$–10). Animals were randomized according to the following groups: (1) Sham, (2) MI, and (3) MI + Enalapril (Enal). All the animals were followed up for 35 days. Enal was administered by gavage at a dose of 10 mg/kg/day.

2.3 Echocardiography

At the end of the protocol, rabbits were weighed and anesthetized with ketamine and xylazine as described above. LV dimensions (wall thickness, cavity dimensions, and areas either in systole or diastole) and ventricular function [ejection fraction (EF) (%), shortening fraction (SF) (%), and cardiac output (ml/min)] were evaluated with a Doppler echocardiography system equipped with an 8-MHz linear transducer (Acuson c256).

2.4 Arterial and cardiac catheterization

Arterial blood pressure and LV function were recorded by using a catheter placed inside of the femoral artery and another catheter placed in the carotid artery and advanced to left ventricle [11]. We measured systolic and diastolic ventricular pressures and its derivative in real time. This data was recorded on a PC provided with platelet analog–digital converter (National Instruments) and software for this purpose.

2.5 Histomorphometric analysis

2.5.1 Quantitative determination of infarct size

After functional determinations, hearts were arrested in diastole with 2 M KCl. The balloon was then refilled with water until it reached a final physiological pressure (10–12 mmHg). Then, hearts were perfused with 10% formaldehyde (pH 7.2), allowing 5 min for fixation, and then remained in formaldehyde with the same volume for 72 h. Hearts were cut in slices from apex to base. Slices from a middle section of the hearts were paraffin embedded, and 5-mm-thick sections were stained with hematoxylin and eosin (H&E) and Masson's trichrome. Slices stained with Masson's trichrome were scanned, and the infarct size was calculated from planimetric measurements using Image Pro-Plus 6.0 software (Media Cybernetics, Silver Spring, MD). The infarct size was calculated as the total length of the scar as a percentage of the total LV circumference, using the average of endocardial and epicardial tracings.

2.5.2 Histology

Hearts from each group at 35 days after surgery were used for histological analysis. After death, hearts were excised from the thorax and immersed in 10% formaldehyde for 72 h. Later, hearts were cut from apex to base and embedded in paraffin, 5-mm serial cuts were made, and sections were stained with H&E and Picrosirius red. Myocyte cross-sectional areas were determined on digitalized images of rhodamine-conjugated lectin-stained sections (WGA no. RL-1022; Vector Laboratories, Burlingame, CA) of paraffin-embedded samples. These digitalized images were obtained using a fluorescence microscope (Olympus BX61) attached to a digital camera and connected to a computer equipped with image analysis software. Outlines of myocyte were traced, and cell areas were measured with Image Pro-Plus 6.0. At least 80 measurable cross-sections of myocyte from the septum were routinely measured [12,13]. In slices stained with Picrosirius red, interstitial collagen deposition was also measured in the septum and scar using the image analysis system described above. The percentage of collagen for each region was calculated by adding the areas corresponding to collagen and dividing by the addition of the areas corresponding to myocyte plus the areas of collagen tissue.

2.6 Statistical analysis

All values are expressed as mean ± S.E.M. Pressure–volume curves were tested by two-way ANOVA for repeated measures followed by Bonferroni's test. One-way ANOVA followed by the Newman–Keuls posttest was also used for comparing individual differences in arterial blood pressure and also for morphometric and histological measurements. $P < .05$ was considered statistically significant.

3 Results

Table 1 shows the general data and the MI size at 5 weeks of evolution. Permanent ligature of the coronary artery produced an infarct that affected 30% of the LV mass in MI and 34% in animals with MI chronically treated with Enal (P = NS). LV mass was between 3.2 ± 0.2 and 2.7 ± 0.2 and no significant difference among the groups was observed.

Mean arterial blood pressure (MBP) remained unchanged in the group of animals with MI compared to Sham, while treatment with Enal reduced MBP by 30% in the group of animals with MI (Fig. 1A, $P < .05$ vs. MI). Fig. 1B–F shows ventricular function assessed by cardiac catheterization. MI significantly reduced contractility evaluated by $+dP/dt_{max}$ (Fig. 1B). Furthermore, diastolic function assessed by LV end-diastolic pressure (LVEDP), $-dP/dt_{max}$, t_{50}, and Tau was clearly impaired in MI group ($P < .05$ MI vs. Sham). However, Enal administration improved diastolic function by decreasing LVEDP (from 8.2 ± 0.2 to 5.1 ± 0.3 mmHg) and increasing the isovolumic relaxation rate as evaluated by t_{50} (from 12.4 ± 0.5 to 9.6 ± 0.8 ms) and Tau (from 19.8 ± 0.8 to 15.3 ± 0.9 ms) indices (Fig. 1C–F, $P < .05$ MI vs. MI + Enal).

We have observed by echocardiography that EF and SF significantly decreased in animals with MI, as it was expected, and this drop was

Table 1
Body weight (BW), LV weight, and infarct size (%)

	Body weight (kg)	LV weight (g)	LV weight/BW (g/g)	Infarct size (%)
Sham	2.8 ± 0.1	8.7 ± 0.4	3.2 ± 0.2	–
MI	2.8 ± 0.1	8.3 ± 0.4	2.8 ± 0.3	30 ± 3.0
MI + Enal	2.6 ± 0.1	6.9 ± 0.4*	2.7 ± 0.2	34 ± 8.1

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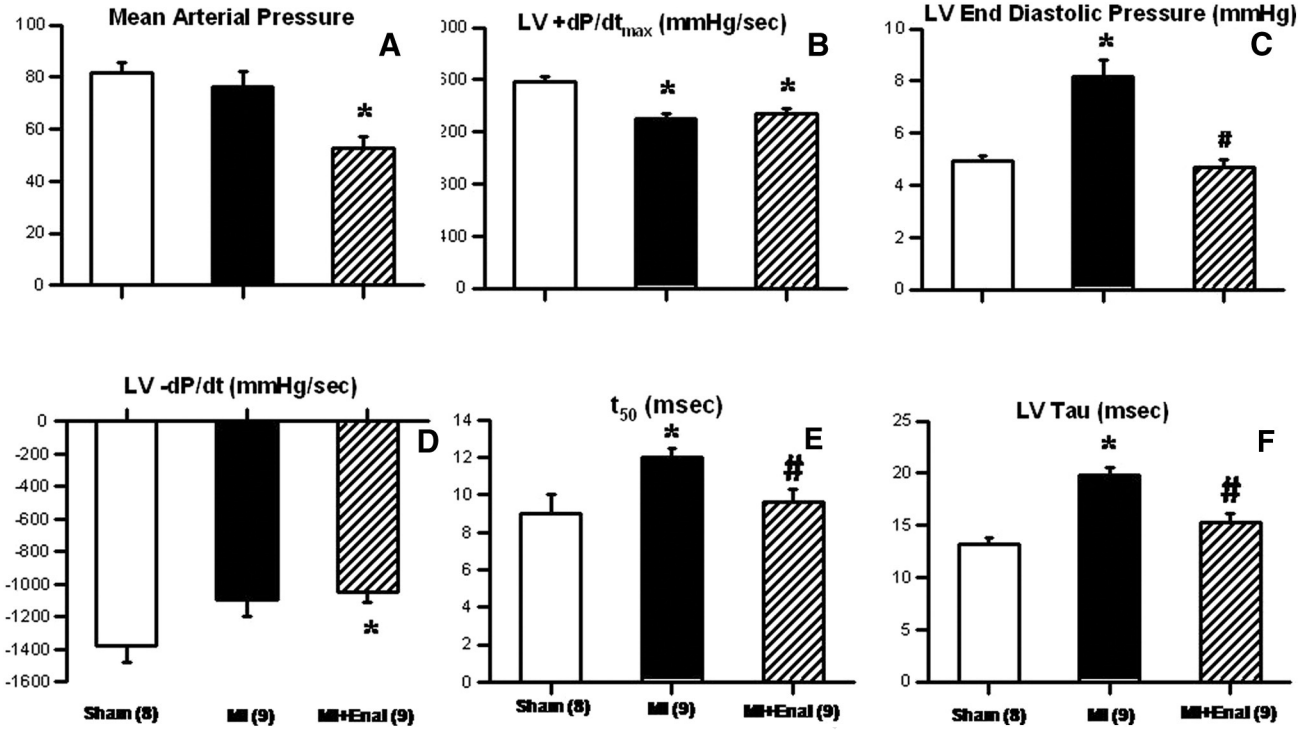

Fig. 1. A mean arterial pressure (A), LV + dP/dt_{max} (B), LVEDP (C), LV − dP/dt_{max} (D), time required for pressure to fall to 50% of its peak value (t_{50}; E), and LV Tau (F) in Sham, MI, and MI + Enal treated rabbits from the onset of infarction. Administration of Enal significantly reduced mean arterial pressure at 35 days of evolution of the MI. The LV + dP/dt_{max} was similarly reduced in both groups with MI. LVEDP and myocardial relaxation rate as measured by LV t_{50} (E) and LV Tau (F) significantly increased in animals with MI. Administration of Enal decreased the LVEDP and improved the LV t_{50} (E) and LV Tau (F) while no changes were observed for − dP/dt_{max}. *P<.05 MI vs. Sham; #P<.05 MI + Enal vs. MI.

prevented by treatment with Enal (Fig. 2). Since Enal did not modify the infarct size, this data suggests that the early administration of Enal improves systolic function.

Myocardial fibrosis was quantified in the septum and in the infarction zones in slices stained with Picrosirius red. In the septum, myocardial fibrosis was significantly increased in MI compared to Sham. This increase was attenuated in animals treated with Enal, while treatment with Enal did not modify fibrosis in MI zone (Fig. 3).

Finally, myocyte hypertrophy evaluated in rhodamine immunolabeled slices was increased in animals with MI and it was significantly reduced in animals treated with Enal (Fig. 4).

4 Discussion

In this study, we found that early administration of Enal to rabbits with permanent ligature of the coronary artery and similar infarct size

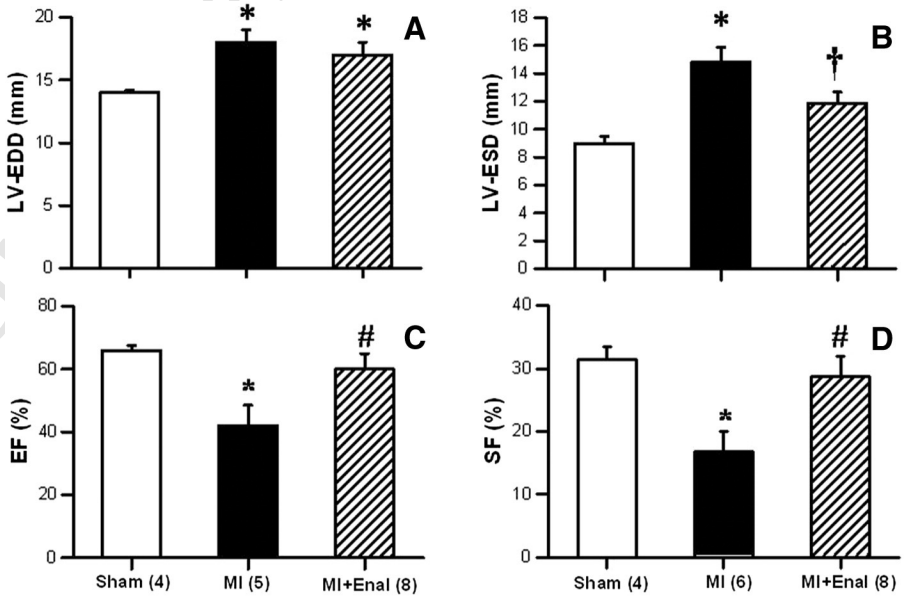

Fig. 2. LV end-diastolic dimension (LVEDD) (A), LVESD (B), EF (C), and SF (D) were evaluated in vivo by echocardiography in Sham, MI, and MI + Enal (Enal) treated rabbits at 35 days post-MI. In MI animals, there was an increase of LVEDD (A) and LVESD (B). The administration of Enal reduced the LVESD, without modifying the LVEDD. As expected, MI group significantly reduced the EF and the SF in relation to Sham. This reduction was significantly reverted with Enal (Enal). *P<.05 vs. Sham; †P<.05 vs. MI, #P<.05 MI + Enal vs. MI.

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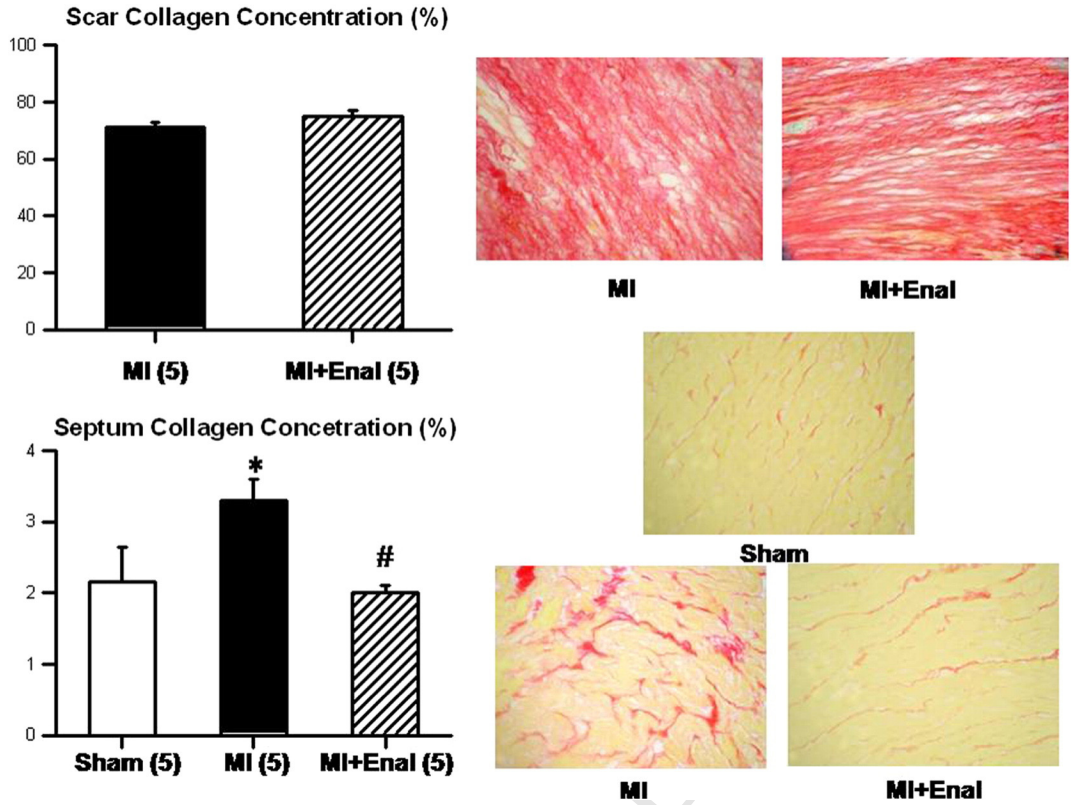

Fig. 3. Collagen concentration in scar (upper panel) and in the septum (lower panel) in Sham, MI, and MI + Enal (Enal) treated animals at 35 days of MI evolution. Treatment with E did not modify collagen concentration in the scar. In the remote zone (septum), the MI significantly increased fibrosis. Such increment was significantly attenuated with Enal. *P<.05 MI vs. Sham; #P<.05 MI + Enal vs. MI.

prevented the development of adverse remodeling and myocardial dysfunction at 35 days post-MI. An important finding of our study is that the chronic administration of Enal entirely prevented not only the systolic dysfunction by increasing EF and SF but also attenuated the diastolic dysfunction by preventing the increase of the end-diastolic pressure and improving the isovolumic relaxation rate. This improvement in the LV function was accompanied by a clear enhancement of remodeling as evidence by a reduction in ventricular cavity size and a decrease of the myocyte cross-sectional area and myocardial fibrosis in the remote areas, although the collagen in the scar was not modified.

In this study, we used an experimental model of MI in rabbits because the histopathological temporal evolution of the MI and ventricular remodeling is similar to that observed in humans [14,15]. However, surprisingly, rabbits have not been used as frequently as other animals to study the role of ACE inhibitors on the MI and ventricular remodeling. We have previously shown that the expression of different components of the RAS in rabbits is also similar to humans and is therefore a suitable experimental model for the study of MI, remodeling, and its modification by agents that block the RAS [14]. In this study, we found that the early administration of Enal from the onset of MI and

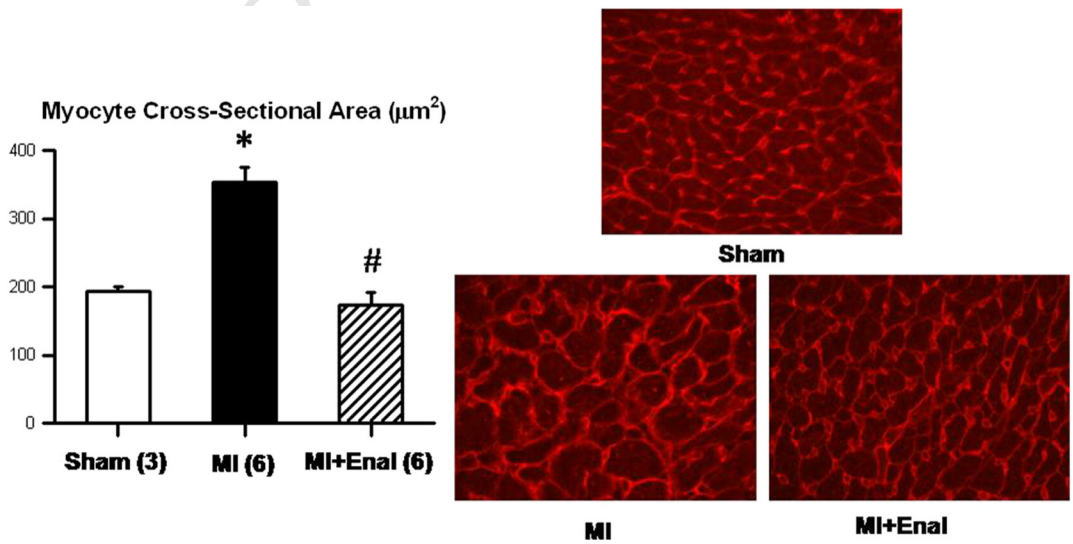

Fig. 4. Transverse sliced area of myocyte in Sham, MI, and MI + Enal (Enal) treated animals at 35 days of MI evolution. MI significantly increased the myocyte hypertrophy and this increase was significantly attenuated with E. *P<.05 MI vs. Sham; #P<.05 MI + Enal vs. MI.

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prolonged during 5 weeks improves ventricular remodeling and function after MI. In a previous study, we have demonstrated that the administration of Losartan adversely modifies remodeling in rabbits, depending on the duration of the treatment and not the time of its beginning [10]. Therefore, given that a possible explanation for adverse remodeling could be the action of Ang II on the AT2 receptors, here we wanted to study if the chronic administration of Enal that prevents the formation of Ang II is able to favorable modify the evolution of LV remodeling and function. The effects of Enal and other ACE inhibitors have been extensively studied in patients, in experimental models, and in heart failure [16–19]. Enal improved mortality and the evolution of patients with HF post-MI. The mechanism of improvement of postinfarct remodeling with ACE inhibition was initially and classically associated in part to peripheral vasodilatation, ventricular unloading, and the attenuation of ventricular dilatation [20]. However, subsequent observations have forced to review this simple concept since ACE inhibitors compared with other vasodilators showed direct tissular effects in addition to vasodilatation. Previous studies from our group suggested that differences in post-MI remodeling due to long-term treatment with Losartan could not be attributed to changes in the MBP. Other vasodilators studied in a canine model of cardiac remodeling have failed to inhibit remodeling [21] whereas ACE inhibitors [21,22] and nitrates [23] did. Therefore, although in our experiments, the reduction of blood pressure might contribute to improve the ventricular remodeling, other actions of ACE inhibitors certainly must be considered as the antiremodeling effect. In our study, Enal partially reduced the LV ventricular dilation since we only found a decrease in LV end-systolic dimension (LVESD). These results are not surprising if we consider that previous studies by Zdrojewski et al. [17] found similar movement of the pressure volume curves in SHR rats treated with Quinapril. However, an important difference between Zdrojewski's research [17] and ours is that they used hypertensive rats and we used normotensive animals at the moment of MI. Recently, Bayir et al. [24] showed that the administration of Ramipril and Valsartan reduced myocardial injury in rats with MI. In this study, we found that Enal did not modify the subsequent myocardial fibrosis in the scar, suggesting that this treatment does not affect the reparation process in the MI zone. This is important when we consider that the reduction of collagen contributes to the increase of ventricular dilation. True defects in the process of reparation and parietal stress are the major determinants of the expansion and the occurrence of adverse clinical events, failure, and death. In our case, the fact that Enal did not affect the reparation process as we had previously observed in animals treated with Losartan would allow us to explain why we did not observe changes in the ventricular cavity.

The chronic administration of Enal to rabbits reduced the myocyte hypertrophy and fibrosis in remote zones. Given that hypertrophy and fibrosis are important markers in adverse remodeling, the prevention of their development would allow explaining, at least partially, the improvement observed in systolic and diastolic function. This reasoning is also sustained by the fact that Enal did not reduce fibrosis in the MI zone, as it was previously mentioned. Another important finding of our study is the beneficial effect of Enal on diastolic function evaluated through LVEDP and isovolumic relaxation rate (Tau and t_{50}). In this case, we observed after Enal administration a decrease in LVEDP as well as an increase in isovolumic relaxation rate. $LV-dP/dt_{max}$ did not reflect the improvement in isovolumic relaxation perhaps because it is also pressure dependent [25]. To further confirm the beneficial effect of Enal on diastolic function, we have included a second isovolumic relaxation index, t_{50}, which showed the same response that of Tau.

While others showed that the administration of Enal reduces LVEDP, at least to our knowledge, it has not been previously shown that this drug can improve isovolumic relaxation in rabbits with MI, constituting a novel finding of our research. The fact that Enal prevented the increase of LVEDP could be explained by a decrease in the myocyte diameter and fibrosis, two major determinants of diastolic dysfunction, while isovolumic relaxation could be explained by intracellular and extracellular components. However, the fact that fibrosis and myocyte hypertrophy in remote zones was prevented by the administration of Enal would explain the improvement in the ventricular stiffness and relaxation. Summarizing, chronic early administration of Enal in rabbits with experimental MI had a favorable effect on remodeling and systolic and diastolic ventricular function by reducing fibrosis and myocyte hypertrophy with no modifications on the reparation process after the MI.

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