Beneficial effects of combination of ACE inhibitor and angiotensin II type 1 receptor blocker on cardiac remodeling in rat myocardial infarction

Yasuhiro Nakamura\textsuperscript{a}, Minoru Yoshiyama\textsuperscript{a,}\textsuperscript{*}, Takashi Omura\textsuperscript{a}, Ken Yoshida\textsuperscript{a}, Yasukatsu Izumi\textsuperscript{a}, Kazuhide Takeuchi\textsuperscript{a}, Shokei Kim\textsuperscript{b}, Hiroshi Iwao\textsuperscript{b}, Junichi Yoshikawa\textsuperscript{a}

\textsuperscript{a}Department of Internal Medicine and Cardiology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan
\textsuperscript{b}Department of Pharmacology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan

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Abstract

Objective: Angiotensin-converting enzyme (ACE) inhibitor and angiotensin II type I receptor blockers (ARB) prevent cardiac remodeling after myocardial infarction (MI). However, it is controversial whether combination therapy of ACE inhibitor and ARB is more effective on cardiac remodeling than each agent alone. In this study, we compared the effects of an ACE inhibitor (temocapril), an ARB (CS-866), and their combination on cardiac remodeling after MI. Methods: Temocapril at 3 or 30 mg/kg/day, CS-866 at 1 or 10 mg/kg/day, or combined temocapril and CS-866 at 1.5 and 0.5 mg/kg/day or at 15 and 5 mg/kg/day, respectively, were administered to rats after MI. At 4 weeks after MI, we assessed hemodynamics, cardiac function by Doppler echocardiography and non-infarcted myocardial mRNA expression. Results: Animals treated with a combination of the two drugs had hemodynamics, heart weights and dimensions similar to the other treated animals. However, the combination of the two drugs suppressed ANP, BNP and other gene expressions related to contractile proteins of fetal type and collagens more effectively than ACE inhibitor or ARB alone. Conclusion: These data suggest that combination of the two drugs, independent of the hemodynamic effect, may improve left ventricular phenotypic change, collagen accumulation and diastolic function.

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Keywords: ACE inhibitors; Adrenergic (ant)agonists; Infarction; Remodeling; Ventricular function

1. Introduction

Myocardial infarction frequently produces left ventricular dilatation associated with myocyte hypertrophy and interstitial fibrosis of the noninfarcted myocardium. These changes in LV geometry, referred to as remodeling, contribute to the development of depressed cardiac performance [1]. Angiotensin-converting enzyme (ACE) inhibitor attenuates LV remodeling, improves the quality of life and decreases the mortality and morbidity of patients with MI and heart failure [2]. Accordingly, it is of critical importance to develop therapeutic strategies that will effectively inhibit the development and progression of LV remodeling and failure after MI. The newer strategies would be adjunctive and/or possibly synergistic with existing therapeutic strategies for treating patients.

Experimental evidence indicates that the influence of ACE inhibitor on LV remodeling may involve both direct angiotensin II effects acting via a variety of angiotensin II receptor subtypes and indirect effects on the kallikrein–kinin system [3,4]. In a rat coronary ligation model, ACE inhibitor and ARB are equally effective in limiting post-
infarction LV remodeling [4,5] and there is no difference in survival at 1 year between rats treated with ACE inhibitor or ARB [6]. Combined ACE inhibitor and ARB provides enhanced benefits in heart failure [7]. Recently, Mankad et al. showed that combination therapy with ACE inhibitor and ARB attenuates postinfarction left ventricular remodeling and systolic dysfunction in an ovine model [8]. On the other hand, Taylor et al. reported that a combined therapy of two drugs has no beneficial effect on postinfarction LV remodeling [9].

The purpose of this study was to examine the effect of combination therapy with the two drugs on diastolic (as well as systolic) abnormalities determined by echocardiography and gene expression encoding proteins potentially implicated in the remodeling process after myocardial infarction.

2. Methods

2.1. Dose-selection, experimental animals and protocol

The administration of CS-866 at 1 and 10 mg/kg/day to cardiomyopathy hamsters resulted in an increase in cardiac HGF concentration and mRNA, and a decrease in cardiac collagen III mRNAs to the same extent [10]. Temocapril at 1 and 10 mg/kg/day and CS-866 at 1 and 10 mg/kg/day could block cardiac remodeling-induced chronic inhibition of NO synthesis [11]. However, in this model, the preventive effect of temocapril on cardiac hypertrophy is less than CS-866. On the other hand, we showed that temocapril at 3 mg/kg/day prevented left ventricular remodeling in myocardial infarcted rats at the same level as candesartan cilextil (ARB) at 1 mg/kg/day [12]. Moreover, Higasihura et al. reported that both temocapril at 1 mg/kg/day and CS-866 at 0.3 mg/kg/day could modulate the muscle fiber composition in a hypertensive and insulin-resistant animal model to the same extent [13]. At the same dose, the effect of CS-866 on cardiovascular disease may be about three times stronger than temocapril. Therefore, in this study we chose temocapril at 3 and 30 mg/kg/day and CS-866 at 1 and 10 mg/kg/day for dose-selection. We used half the monotherapy dose of each in the combination therapy of two drugs.

Male Wistar rats weighing 290 to 310 g were purchased from Clea Japan (Osaka, Japan). MI was produced by ligation of the left coronary artery as previously described [14]. The same surgical procedures were performed on a control group of rats except that the suture around the coronary artery was not tied. Rats that survived after coronary ligation were randomly divided into groups and treated with (1) vehicle (0.5% carboxymethylcellulose solution), (2) temocapril 3 mg/kg/day, (3) temocapril 30 mg/kg/day, (4) CS-866 1 mg/kg/day, (5) CS-866 10 mg/kg/day, (6) combined temocapril 1.5 mg/kg/day and CS-866 0.5 mg/kg/day and (7) combined temocapril 15 mg/kg/day and CS-866 5 mg/kg/day within 6 h after coronary ligation. All drugs were orally given to MI rats by gastric gavage once a day for 4 weeks after MI. We used sham-operation rats as controls. We also administered vehicle (0.5% carboxymethylcellulose solution) to myocardial infarcted rats. The vehicle-treated group was used for obtaining specimens from animals that did not receive pharmacotherapy.

2.2. Doppler-echocardiographic studies and physiological studies

Transthoracic echocardiographic studies were performed as previously described in detail [5]. In brief, rats were lightly anesthetized with intraperitoneal injection of ketamine HCl and xylazine. Echocardiograms were performed using an echocardiographic system equipped with a 12.0-MHz phased-array transducer (SONOS 5500; Philips Medical System, Best, The Netherlands). Two-dimensional short-axis view of the left ventricle and M-mode tracings were recorded through the anterior and posterior LV walls at the papillary muscle level to measure LV end-diastolic dimension (LVEDD). LV ejection fraction (LVEF) was measured by modified Simpson’s method, which uses a 4-chamber view. Pulse-wave Doppler spectra (E and A waves velocity) of mitral inflow were recorded from the apical 4-chamber view, with the sample volume placed near the tips of the mitral leaflets. All Doppler spectra were recorded on paper at 100 mm/s and analyzed off-line.

The method of hemodynamics measurement was previously described in detail [14]. In brief, LV pressure was recorded by inserting a polyethylene-tubing catheter (0.58-mm internal diameter, PE-50) into the right carotid artery and advancing it into the left ventricle. Water-filled catheters were connected to the tubing connected to a water-filled pressure transducer. The pressures were recorded on a physiological recorder, while rats were allowed to breathe spontaneously. LV end-diastolic pressure (LVEDP) was obtained by averaging the values for 10 beats. Myocardial infarct size was measured as previously described [14]. Rats with an infarct size of <30% were excluded from analysis because they did not show typical LV remodeling. After determination of infarct size, the heart was immediately excised and septal myocardium was dissected as non-infarcted myocardium. The specimens were immediately frozen and stored at −80 °C until use.

2.3. RNA preparation and Northern blot analysis

All procedures were performed as described in detail in our previous report [5]. In brief, total RNA was isolated from septal myocardium by the guanidium thiocyanate–phenol–chloroform method, and 20 μg of total RNA samples were subjected to 1% agarose gel electrophoresis, transferred to nylon membrane, and hybridization was carried out with (32P)-dCTP-labeled cDNA probe for atrial
natriuretic peptide (ANP), brain natriuretic peptide (BNP), transforming growth factor β1 (TGF-β1), collagen type I and III, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), or with (γ-32P)-ATP-labeled oligonucleotide for α-myosin heavy chain (α-MHC), β-myosin heavy chain (β-MHC), α-skeletal actin (α-Ske A), and α-cardiac actin (α-Car A). The densities of an individual mRNA band were measured by using a bioimaging analyzer (BAS-2000, Fuji Photo Film, Tokyo, Japan).

2.4. Statistics

Results were expressed as mean±S.E.M. Statistical significance was determined using ANOVA and Duncan’s multiple range test. Differences were considered statistically significant at P<0.05.

3. Results

3.1. Changes in hemodynamics and ventricular weight

As shown in Table 1, all drugs slightly, but not significantly, lowered mean blood pressure in rats with MI. LVEDP was significantly higher in rats with MI than in controls (P<0.01). Temocapril, CS-866 and their combination significantly reduced LVEDP post MI (P<0.01). There was no significant difference in LVEDP among the treatment groups. LV weight, corrected for body weight (BW), in rats with MI was significantly reduced by all drug treatments (P<0.01). Right ventricular (RV) weight, corrected for BW, in rats with MI was significantly higher than that in controls (P<0.01). Compared with untreated MI, RV weight was significantly reduced by temocapril at 3 mg/kg/day (P<0.05) and 30 mg/kg/day (P<0.01), and by CS-866 at 1 and 10 mg/kg/day (P<0.01). Combination treatment tended to reduce RV weight more than either agent alone. There was no significant difference in MI size among the groups.

3.2. Doppler echocardiographic assessment

Echocardiographic assessments of LV geometry and function at 4 weeks are shown in Table 2. LV end-diastolic dimensions (LVDd) and LV end-diastolic volume (LVEDV) significantly increased in vehicle rats with MI compared with control rats (P<0.01). Both LVDd and LVEDV in rats with MI was significantly reduced by all drug treatment (P<0.01). Vehicle rats with MI had significant systolic dysfunction, as evidenced by decreased LV ejection fraction at 4 weeks.

Table 1
Hemodynamics and ventricular weights

<table>
<thead>
<tr>
<th>Control</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
</tr>
<tr>
<td>n</td>
<td>8</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>363±7</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>118±5</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>3.8±0.3**</td>
</tr>
<tr>
<td>BW (g)</td>
<td>362±18</td>
</tr>
<tr>
<td>LV weight (mg/g)</td>
<td>0.58±0.02**</td>
</tr>
<tr>
<td>MI size (%)</td>
<td>41±3</td>
</tr>
</tbody>
</table>

Mean BP, mean blood pressure; LVEDP, left ventricular end-diastolic pressure; BW, body weight; LV weight, left ventricular weight/body weight; RV weight, right ventricular weight/body weight; MI size, myocardial infarction size. *P<0.05 vs. MI, **P<0.01 vs. MI. Values are mean±S.E.M.

Table 2
Doppler echocardiographic assessment of left ventricular geometry and function

<table>
<thead>
<tr>
<th>Control</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>6.5±0.4**</td>
</tr>
<tr>
<td>LVEDV (µl)</td>
<td>279±14**</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>62±4**</td>
</tr>
<tr>
<td>E wave velocity (cm/s)</td>
<td>62±3**</td>
</tr>
<tr>
<td>A wave velocity (cm/s)</td>
<td>42±3**</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5±0.1**</td>
</tr>
<tr>
<td>E deceleration (m/s²)</td>
<td>15±1**</td>
</tr>
</tbody>
</table>

LVDd, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction. *P<0.05 vs. MI, **P<0.01 vs. MI. Values are mean±S.E.M.
ejection fraction (LVEF) compared with control rats ($P<0.01$). LVEF in rats with MI was significantly improved by all drug treatment ($P<0.01$). However, there was no significant difference in LVDd, LVEDV and LVEF among all treated groups.

Examples of pulse-wave Doppler recordings of mitral inflow from the seven groups are shown in Fig. 1. Compared with the control group, MI group had significant diastolic dysfunction ($P<0.01$), as defined by increased early rapid filling wave (E wave) velocity, decreased late filling wave due to atrial contraction (A-wave) velocity, an increased ratio of E wave to A wave (E/A ratio) and a decelerated E wave rate. All drug treatments significantly improved the diastolic function ($P<0.01$). Furthermore, the improvement in diastolic function by combination of temocapril and CS-866 was significantly greater than that by any other drug treatments.

3.3. Cardiac gene expression after myocardial infarction

The results of cardiac gene expression at 4 weeks are shown in Fig. 2 and Table 3. At 4 weeks after MI, $\beta$-MHC, $\alpha$-Ske A, ANP, BNP and TGF-$\beta$1, and collagen type I and III mRNA expression significantly increased (3.1-, 3.9-, 5.0-, 10.1-, 2.0-, 10.9- and 8.2-fold, respectively, $P<0.01$) in the non-infarcted myocardium. Temocapril at 3 and 30 mg/kg/day, and CS-866 at 1 and 10 mg/kg/day significantly attenuated the increased expression of $\beta$-MHC, $\alpha$-Ske A, ANP, BNP, TGF-$\beta$1 and collagen type I and III mRNA ($P<0.01$). Moreover, the combination of ACE inhibitor and ARB was more effective than either agent alone in attenuating expression of $\beta$-MHC, $\alpha$-Ske A, ANP, BNP ($P<0.01$), TGF-$\beta$1 and collagen type I and III mRNA ($P<0.05$). Thus, the combination of ACE inhibitor and ARB might prevent the increase in cardiac gene expression after MI more than either agent alone.

4. Discussion

Accumulating evidence suggests that the cardiac renin–angiotensin system (RAS) is activated during the left ventricular (LV) remodeling process after acute myocardial infarction. The results of cardiac gene expression at 4 weeks are shown in Fig. 2 and Table 3. At 4 weeks after MI, $\beta$-MHC, $\alpha$-Ske A, ANP, BNP and TGF-$\beta$1, and collagen type I and III mRNA expression significantly increased (3.1-, 3.9-, 5.0-, 10.1-, 2.0-, 10.9- and 8.2-fold, respectively, $P<0.01$) in the non-infarcted myocardium. Temocapril at 3 and 30 mg/kg/day, and CS-866 at 1 and 10 mg/kg/day significantly attenuated the increased expression of $\beta$-MHC, $\alpha$-Ske A, ANP, BNP, TGF-$\beta$1 and collagen type I and III mRNA ($P<0.01$). Moreover, the combination of ACE inhibitor and ARB was more effective than either agent alone in attenuating expression of $\beta$-MHC, $\alpha$-Ske A, ANP, BNP ($P<0.01$), TGF-$\beta$1 and collagen type I and III mRNA ($P<0.05$). Thus, the combination of ACE inhibitor and ARB might prevent the increase in cardiac gene expression after MI more than either agent alone.

Fig. 1. Examples of pulse-wave Doppler spectra of mitral inflow from the sham operated rat (control), myocardial infarcted (MI) rat administered with vehicle, MI rat treated with temocapril at 3 or 30 mg/kg/day (ACEI (3) or ACEI (30), respectively), MI rat treated with CS-866 at 1 or 10 mg/kg/day (ARB (1) or ARB (10), respectively), the combination with temocapril at 1.5 and CS-866 at 0.5 mg/kg/day (ACEI (1.5)+ARB (0.5)), and the combination with temocapril at 5 and CS-866 at 15 mg/kg/day (ACEI (5)+ARB (15)).
in Fig. 2. Autoradiograms of Northern blot analysis showing mRNA expression of ANP, BNP, α-MHC, β-MHC, TGF-β1, α-Ske A, α-Car A, collagen I and III and GAPDH in non-infarcted septum at 4 weeks after MI. C, control; MI, myocardial infarcted rats; L, combination with temocapril at 1.5 and CS-866 at 0.5 mg/kg/day; H, combination with temocapril at 5 and CS-866 at 15 mg/kg/day. Other abbreviations as in Fig. 1.

infarction (MI) [2,14]. The result of the process may be advanced LV systolic and diastolic dysfunction. Recently, accumulating evidence supports the notion that angiotensin II type I receptor blocker (ARB) has nearly the same favorable effects as ACE inhibitor on cardiac hypertrophy, remodeling and heart failure [5,15,16]. However, pharmacological profiles are substantially different between ARB and ACE inhibitor, because ARB can inhibit the action of angiotensin II (Ang II) generated through not only ACE but also alternative pathways of Ang II formation [17], whereas ACE inhibitors block bradykinin metabolism [3,18]. Therefore, combination therapy with ACE inhibitor and ARB are reported to have benefits beyond those of either agent alone. A recent study shows that the combination of ACE inhibitor and ARB improves LV phenotypic change, increased LV collagen accumulation, diastolic dysfunction, and survival in rat heart failure model more effectively than either agent alone [19]. In the present study, we compared the effects of ACE inhibitor (temocapril), ARB (CS-866), and a combination of these two agents assessed by Doppler echocardiography and cardiac gene expression associated with cardiac remodeling in rats with MI. We obtained important evidence that the combination of ACE inhibitor and ARB improves LV phenotypic

Table 3
Gene expression after myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Control (5)</th>
<th>ACEI (3)</th>
<th>ACEI (30)</th>
<th>ARB (1)</th>
<th>ARB (10)</th>
<th>ACEI (1.5)</th>
<th>ACEI (1.5) + ARB (0.5)</th>
<th>ACEI (1.5) + ARB (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-MHC</td>
<td>1.00±0.06</td>
<td>0.96±0.07</td>
<td>1.01±0.07</td>
<td>0.92±0.05</td>
<td>0.97±0.05</td>
<td>0.92±0.06</td>
<td>0.91±0.04</td>
<td>0.96±0.06</td>
</tr>
<tr>
<td>β-MHC</td>
<td>1.00±0.04*</td>
<td>3.08±0.23</td>
<td>2.51±0.18*</td>
<td>2.48±0.13*</td>
<td>2.43±0.14*</td>
<td>2.29±0.17*</td>
<td>1.69±0.10</td>
<td>1.71±0.11*</td>
</tr>
<tr>
<td>α-Cardiac actin</td>
<td>1.00±0.05</td>
<td>0.98±0.06</td>
<td>0.94±0.07</td>
<td>0.95±0.03</td>
<td>0.94±0.06</td>
<td>0.94±0.06</td>
<td>1.02±0.07</td>
<td>1.03±0.06</td>
</tr>
<tr>
<td>α-Skeletal actin</td>
<td>1.00±0.07*</td>
<td>3.91±0.22</td>
<td>2.84±0.20*</td>
<td>2.97±0.19*</td>
<td>2.98±0.14*</td>
<td>2.85±0.09</td>
<td>2.01±0.13*</td>
<td>2.10±0.10*</td>
</tr>
<tr>
<td>ANP</td>
<td>1.00±0.06*</td>
<td>5.00±0.29</td>
<td>3.52±0.25*</td>
<td>3.60±0.25*</td>
<td>3.62±0.22*</td>
<td>3.71±0.17*</td>
<td>2.00±0.14</td>
<td>1.83±0.12*</td>
</tr>
<tr>
<td>BNP</td>
<td>1.00±0.05*</td>
<td>10.10±0.94</td>
<td>4.30±0.31*</td>
<td>4.13±0.37*</td>
<td>4.17±0.26*</td>
<td>4.41±0.30*</td>
<td>2.25±0.25</td>
<td>2.28±0.26*</td>
</tr>
<tr>
<td>Collagen I</td>
<td>1.00±0.06*</td>
<td>10.93±0.79</td>
<td>8.64±0.56*</td>
<td>7.48±0.55*</td>
<td>8.02±0.51*</td>
<td>7.72±0.45*</td>
<td>5.87±0.39</td>
<td>5.86±0.27*</td>
</tr>
<tr>
<td>Collagen III</td>
<td>1.00±0.06*</td>
<td>8.19±0.50</td>
<td>5.98±0.36*</td>
<td>5.46±0.40*</td>
<td>5.66±0.41*</td>
<td>5.90±0.50*</td>
<td>4.10±0.30**</td>
<td>4.25±0.26**</td>
</tr>
<tr>
<td>TGF-β</td>
<td>1.00±0.10**</td>
<td>1.95±0.20</td>
<td>1.54±0.14*</td>
<td>1.49±0.11**</td>
<td>1.50±0.16*</td>
<td>1.30±0.22*</td>
<td>1.16±0.12**</td>
<td>1.12±0.08**</td>
</tr>
</tbody>
</table>

*P<0.05 vs. MI. **P<0.01 vs. MI. Values are mean±S.E.M.
change, increased LV collagen accumulation, and diastolic dysfunction in LV remodeling after MI.

Doppler echocardiography is currently the primary technique for evaluating left ventricular diastolic function. Increased E-wave velocity, decreased peak A-wave velocity (or absent A wave), and rapid E-wave deceleration were observed in our rats, and these flow patterns were similar to transmitral flow profiles observed in patients with heart failure with restrictive patterns. ACE inhibitor, ARB and these agents in combination decreased the E/A ratio and E-wave deceleration rate. Long-term ACE inhibitor therapy could prevent changes in left ventricular diastolic properties in patients with depressed ejection fraction [20]. Improvement of diastolic filling pattern is caused by preload, afterload reduction, improvement in left ventricular relaxation, or decrease in passive elastic properties. Our data do not directly answer the question of whether the change in left ventricle filling patterns are due to changes in myocardial properties, changes in left ventricle loading conditions, or both. The major limitation of diastolic assessment by echo-Doppler techniques lies in the load-dependency of the E and A waves and their ratio.

When viewed in the context of previous studies using isolated muscle preparations from the same animal model of heart failure [21,22], the improvement in diastolic filling pattern that accompanies inhibition of the renin–angiotensin system results from a combination of effects on left ventricular preload and afterload as well as left ventricular chamber properties. LVEDP was not statistically significant between the treatment arms, however, improvement of E/A waves ratio and E decelerations rate differed. This means that a combination more effectively prevents an increase in left ventricular relaxation, a decrease in passive elastic properties than each drug alone. Combination therapy with two agents may be a useful therapeutic strategy for treatment of diastolic dysfunction. Animals treated with a combination of the two drugs had hemodynamics, heart weights and dimensions similar to the other treated animals. The combination of the two drugs suppressed ANP, BNP, TGF-β1, and collagen gene expressions, and other gene expressions related to contractile proteins of fetal type and collagens more effectively than ACE inhibitor or ARB alone. These data suggest that combination of the two drugs, independent of the hemodynamic effect, may improve left ventricular phenotypic change, collagen accumulation and diastolic function. We suppose that the combination of these two agents is more beneficial than monotherapy for prevention of left ventricular remodeling.

TGF-β1 appears to cause cellular hypertrophy and stimulate the production of ECM such as fibronectin, collagen and laminin [23,24]. Furthermore, the addition of TGF-β1 to cultured cardiac myocytes leads to the phenotypic modulation of myocytes, as shown by the induction of the gene expression of fetal contractile proteins [25]. Hanatani et al. showed that TGF-β1 increased in non-infarcted myocardium after myocardial infarction. Thus, TGF-β1 may be responsible for the development of LV remodeling [26]. Kim et al. reported that TGF-β1 mRNA expression in cardiac hypertrophy of SHRSP is prevented by ACE inhibitor or ARB [27]. In our study, a combination therapy with ACE inhibitor and ARB prevented TGF-β1 mRNA expression as well as other mRNAs referred to as remodeling.

Solid evidence indicates that angiotensin II directly stimulates LV ANP, BNP, TGF-β1, and collagen gene expression via AT1 receptor independently of its hemodynamic effect [28,29]. Therefore, in the present study, the mechanism underlying the greater suppression of LV ANP gene expression, TGF-β1, and collagen accumulation in myocardial infarcted rats by combined ACE inhibitor and ARB than either agent alone may be explained by a more potent inhibition of angiotensin II-mediated AT1 receptor activation itself. However, ACE inhibitor increases tissue bradykinin accumulation, and the bradykinin has antigrowth effects and reduces vasomotor tone [3]. Therefore, the possibility cannot be excluded that the accumulation of bradykinin by ACE inhibitor might have participated in the present beneficial effects of the combination therapy in myocardial infarcted rats. Conversely, unlike ACEI, ARB increases circulating angiotensin II levels, leading the stimulation of AT2 receptor, which has antigrowth effects [15,30]. However, unlike treatment with ARB alone, the combination with ACE inhibitor suppresses plasma angiotensin II elevation induced by ARB, indicating that AT2 receptor activation caused by ARB alone is nullified by the combination with ACE inhibitor. Therefore, it is unlikely that AT2 receptor might have contributed to the beneficial effects of the combination therapy in the present study. However, further work is needed to elucidate details of the mechanism responsible for the beneficial effects of the combination therapy on LV remodeling.

We excluded infarcts <30% of ventricular myocardium from the analysis. The reason is that we can easily present the difference of the drug effect on the remodeling change, the extent of which is related to infarct size. However, the majority of both clinical and experimental infarcts are in the range of 20–30%. Our myocardial infarcted rat model is a large size of myocardial infarction. Therefore, it is not certain whether our combination therapy is useful for myocardial infarction in general. We missed having a useful ‘bench-to-bedside’ value in our experiments.

In conclusion, we obtained important evidence that a combination of ACE inhibitor and ARB improves LV phenotypic change, increased LV collagen accumulation, and diastolic dysfunction in LV remodeling after MI.

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References


