Long acting calcium antagonist amlodipine prevents left ventricular remodeling after myocardial infarction in rats

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Abstract

Objective: The purpose of this study was to examine the effect of amlodipine, a long-acting calcium antagonist, on the left ventricular remodeling, including systolic and diastolic dysfunction, the change of cardiac gene expression in the myocardial infarcted rats MI.

Methods: On the first day after myocardial infarction, the animals were randomly assigned to amlodipine treatment (n = 8) or untreated groups MI; n = 9. We then performed Doppler-echocardiographic examinations and measured the hemodynamics at four weeks after myocardial infarction. Following these measurements, their cardiac mRNA was analyzed.

Results: Left ventricular end-diastolic pressure LVEDP and central venous pressure CVP increased to 22 ± 1 mmHg and 5 ± 1 mmHg. Amlodipine reduced LVEDP and CVP to 15 ± 1 mmHg (P < 0.01) and 3 ± 0 mmHg (P < 0.01). The weight of right ventricle in MI was significantly larger than in the control rats Control; 0.48 ± 0.01 g/kg, MI; 0.79 ± 0.04 g/kg, P < 0.01. Left ventricular end-diastolic dimension LVDd in MI increased to 10.3 ± 0.3 mm (P < 0.01) (Control; 6.2 ± 0.3 mm). Amlodipine prevented an increase of the weight of right ventricle (0.62 ± 0.03 g/kg, P < 0.01) and LVDd (7.9 ± 0.2 mm, P < 0.01 to MI). The rats in MI showed systolic dysfunction shown by the decreased fractional shortening (Control; 31 ± 2% versus MI; 15 ± 1%, P < 0.01), and diastolic dysfunction shown by E wave deceleration rate (Control; 18.1 ± 2.0 m/s², MI; 32.6 ± 2.1 m/s², P < 0.01). Amlodipine significantly prevented systolic and diastolic dysfunction. The increases in β-MHC, α-skeletal actin, and ANP mRNAs in the non-infarcted left ventricle and right ventricle at four weeks after the myocardial infarction were all significantly suppressed by the treatment with amlodipine. On the other hand, depressed α-MHC was restored to normal levels by amlodipine in both regions.

Conclusions: Amlodipine prevents the left ventricular remodeling process accompanied by systolic and diastolic dysfunction, and inhibits abnormal cardiac gene expression after myocardial infarction. © 1998 Elsevier Science B.V.

Keywords: Ventricular remodeling; Myocardial infarction; Calcium channel antagonists; Echocardiography; Gene expression

1. Introduction

The global alterations of left ventricular architecture characterizing left ventricular postinfarct remodeling consist of ventricular dilatation accompanied by hypertrophy, which occurs in the course of weeks to months [1,2]. Although this process probably constitutes a compensatory response to acute loss of myocardial mass, it is associated with progressive chamber dysfunction and an increased incidence of sudden death and congestive heart failure [3]. The administration of angiotensin-converting enzyme inhibitor has been shown to prevent left ventricular remodeling and to prolong survival in experimental myocardial infarction and in patients after myocardial infarction [4–7]. However, other vasodilator agents, including calcium channel antagonists, do not clearly show the same beneficial effects on left ventricular remodeling after myocardial infarction.

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Amlodipine, so called third generation of calcium channel antagonists, appears to have fewer negative inotropic effects than previous other calcium antagonists [8–10]. Its slow onset of action and plasma half-life of more than 30 h do not activate the neurohumoral system [11]. Recently, amlodipine has reported to improve the prognosis of non-ischemic heart failure [12]. Amlodipine is expected to become a representative calcium channel antagonist for the treatment of ischemic heart disease and also have other benefits for the treatment of cardiovascular disease. The purpose of this study was to assess the effect of amlodipine on left ventricular remodeling after myocardial infarction in the rat. Left ventricular geometry and cardiac function were assessed by Doppler-echocardiography and cardiac gene expression of contractile protein and collagen in non-infarcted left ventricle and right ventricle by Northern blot analysis.

2. Materials and methods

Each animal received human care in compliance with the Principles of Laboratory Animal Care of the National Society of Medical Research and the Guide for the Care and Use of Laboratory Animals of the National Academy of Sciences.

2.1. Experimental protocol

Male Wistar rats, weighing 290–310 g (Clea Japan, Osaka, Japan) were used in the present experiments. Rats were anesthetized by intraperitoneal injection of pentobarbital sodium (35 mg/kg, i.p.) and xylocaine (10 mg/kg, i.p.), and following intratracheal intubation, a left thoracotomy was performed under volume-controlled mechanical ventilation (tidal volume 3.0 ml, respiration rate 60 cycle/min). The heart was accessed from the thorax, and a ligature with a 6-0 prolene suture was placed around the proximal left anterior descending coronary artery. The chest was then closed. The same surgical procedures were also performed in sham-operated rats (n = 7), except that the suture around the coronary artery was not tied. About ten percent of rats died during operation and about five percent died for 24 h after operation. The rate of rats with more than 20% myocardial infarct size was about 90% in all myocardial infarcted rats. Rats with myocardial infarction surviving the operation for 24 h were randomly separated into amlodipine treated and untreated groups. Amlodipine caused dose-related reductions in blood pressure and the dosage of 10 mg/kg/day of amlodipine produced a substantial antihypertensive effect in SHR's with established hypertension [13], and we used 10 mg/kg/day of amlodipine to myocardial infarcted rats.

The rats of the treated group were administered amlodipine orally (10 mg/kg), in a volume of 2 ml/kg, by gastric gavage once per day for four weeks (n = 8). The untreated group received a vehicle (5% gum arabic solution) in the same manner as the amlodipine (n = 9). The left ventricular remodeling progresses with time and cardiac morphological alterations, including left ventricular cavity dilatation, expansion of infarct zone and the hypertrophy of non-ischemic myocardium, become apparent at 4 weeks after MI and these changes are still ongoing [14]. We considered that analyzing cardiac function and gene expressions is suitable for hearts at 4 weeks after MI. Before the treatment, body weight and blood pressure in these groups did not differ significantly. Systolic blood pressure of the conscious rats was measured by the tail-cuff method using a sphygmomanometer before starting treatment (Riken Development, Tokyo, Japan).

2.2. Doppler-echocardiographic studies

Litwin reported the Doppler-echocardiographic method in the experimental model of MI in rats in detail [15]. We describe the method of Doppler-echocardiographic studies briefly.

Rats were lightly anesthetized with intraperitoneal ketamine HCl (25 mg/kg to 50 mg/kg) and xylazine (5 mg/kg to 10 mg/kg). Echocardiograms were performed using a commercially available echocardiographic system equipped with a 7.5 MHz phased-array transducer (Hewlett Packard, Andover, Mass). A two-dimensional short-axis view of the left ventricle was obtained at the level of the papillary muscles. M-mode tracings were recorded through the anterior and posterior left ventricular walls at a paper speed of 100 mm/s. The anterior and posterior end-diastolic and end-systolic wall thickness and left ventricular internal dimensions and parameters of cardiac functions were measured by the leading-edge method of the American Society for Echocardiology (ASE) from at least three consecutive cardiac cycles on the M-mode tracings.

Pulsed-wave Doppler spectra of mitral inflow were recorded from the apical four-chamber view, with the sample volume placed near the tips of the mitral leaflets and adjusted to the position at which velocity was maximal and the flow pattern laminar. The sample volume was set at the smallest size available. The left atrium was then examined with pulsed-wave Doppler for the presence of mitral regurgitation. All Doppler spectra were recorded on paper at 100 mm/s and analyzed off-line as previously described. The numbers represent the mean of at least three consecutive cardiac cycles.

2.3. Hemodynamic studies

One day after the echocardiogram, the rats were anesthetized by intraperitoneal injection of ketamine HCl (25–50 mg/kg) and xylazine (5–10 mg/kg). Amlodipine was administered about 6 h before hemodynamics in rats were measured. Aortic and left ventricular pressure were recorded by inserting a polyethylene tubing catheter (0.58
mm internal diameter, PE-50) into the right carotid artery and advanced into the aorta and then into the left ventricle. Central venous pressure was measured by cannulating the right external jugular vein with a PE-50 tubing catheter. Water-filled catheters were connected to the polyethylene tubing (0.76 mm internal diameter, PE-60) connected to a water-filled pressure transducer (Model P23 ID, Gould, California, USA). With rats breathing spontaneously, pressures were recorded on a physiological recorder (Polygraph MIC-9800 and Thermal Recorder RF-85, Fukuda Denshi, Tokyo, Japan). Heart rate was determined from the tracing of aortic pressure.

Following these measurements rats were decapitated and the heart removed. The size of the myocardial infarct was measured, as previously described [16]. LVEDP did not increase in rats with infarct size less than 20% and these were excluded from the experiments. Rats with less than 20% of infarct size were excluded from analysis. Following determination of infarct size, the left ventricle was divided into the non-infarcted left ventricle portions and other portions, including the scar tissue. After weighing, the tissues were rapidly frozen in liquid nitrogen and stored at −80°C. All procedures were carried out within three min.

2.4. Oligonucleotide and cDNA probes

We used synthetic oligonucleotide probes complementary to the unique 3′ untranslated regions of the two MHC and the two α-actin mRNAs, as previously described [17]. The sequence of the oligonucleotide probes used were as follows:

- α-MHC, 5′-TTGTGGGATAGCAACAGCGA-3′;
- β-MHC, 5′-GTCTCAGGGCTTCACAGG-3′;
- α-skeletal actin, 5′-GCAACCATAGCGAGTTGC-3′;
- α-cardiac actin, 5′-TGACGTTGTAACAAAAC-3′.

In addition, to monitor the RNA content of the various lanes, we hybridized the blots with 24-base oligonucleotide complementary to rat 18S ribosomal RNA. The oligonucleotide probes were labeled with (γ-32P)-ATP (6000 Ci/mM) at the 5′ end using T4 polynucleotide kinase, and the labeled probes were purified by chromatography on the Bio-Spin 6 column (Bio-Rad, Richmond, CA).

The cDNA probes were used rat α1(I) collagen cDNA (1.3 kb PstI/BamHI fragment) [18], mouse α1(III) collagen cDNA (1.8 kb EcoRI/EcoRI fragment) [19], rat ANP cDNA (0.825 kb fragment) [17]. The cDNA probes were labeled with (32P)-dCTP (specific activity 3000 Ci/mM, New England Nuclear, Boston, MA) by the random primer extension method, using a Random Primer DNA Labeling Kit (Takara, Kyoto, Japan).

2.5. Northern blot hybridization

The method of RNA extraction was previously described in detail [20]. The RNA concentration was spectrophotometrically determined at 260 nm. Twenty μg of total RNA was denatured by incubating it with 1 M deionized glyoxal and 50% dimethyl sulfoxide at 50°C for 1 h, electrophoresed on 1% agarose gel and transferred to a nylon membrane (GeneScreen Plus, E.I. du Pont de Nemours, NEN products, Boston, USA), as previously described [20]. The 28S and 18S ribosomal RNAs in gels were stained with ethidium bromide to demonstrate the integrity of applied RNA and verify that the same amount of RNA was applied to each lane. The method of Northern blot analysis using the oligonucleotide probe and a specific cDNA probe was previously described [17].

2.6. Quantification of mRNA

To evaluate mRNA levels, an optical scanner (EPSON GT-8000, Seiko, Tokyo, Japan) was utilized for digitizing autoradiograms. The autoradiogram bands in the digitized image were measured for their density with the use of the public domain NIH image program and a computer (Macintosh LC-III, Apple Computer, USA), as described. For all RNA samples, the density of an individual mRNA band was divided by that of the 18S ribosomal RNA band, to correct for differences in RNA loading and/or transfer.

2.7. Statistics

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

3. Results

3.1. Effect of amlodipine on hemodynamics

Table 1 shows no significant differences in body weight and heart rate between the control rats (Control) and rats with myocardial infarction treated with either the vehicle

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 7)</th>
<th>MI (n = 9)</th>
<th>MI + amlodipine (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>386 ± 5</td>
<td>391 ± 5</td>
<td>378 ± 4</td>
</tr>
<tr>
<td>LV weight, g/kg</td>
<td>2.04 ± 0.04</td>
<td>2.09 ± 0.05</td>
<td>1.94 ± 0.041</td>
</tr>
<tr>
<td>RV weight, g/kg</td>
<td>0.48 ± 0.01</td>
<td>0.79 ± 0.04*</td>
<td>0.62 ± 0.03***</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>245 ± 8</td>
<td>259 ± 11</td>
<td>243 ± 6</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>119 ± 2</td>
<td>109 ± 3*</td>
<td>99 ± 2**</td>
</tr>
<tr>
<td>LVSP, mm Hg</td>
<td>140 ± 5</td>
<td>127 ± 4*</td>
<td>114 ± 3***</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>6 ± 0</td>
<td>22 ± 1*</td>
<td>15 ± 1**</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>2 ± 0</td>
<td>5 ± 1**</td>
<td>3 ± 0</td>
</tr>
<tr>
<td>MI size, %</td>
<td>-</td>
<td>39 ± 3</td>
<td>41 ± 2</td>
</tr>
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</table>

* P < 0.05, ** P < 0.01 vs. control, 1P < 0.05, 1P < 0.01 vs. MI.
Fig. 1. Examples of M-mode echocardiograms from sham-operated Control, myocardial-infarcted rats MI and myocardial-infarcted rats treated with amlodipine. AW indicates anterior wall; and PW indicates posterior wall. Note the left ventricular cavity dilatation, thinning, and akinesis of the anterior wall in rats with MI. Amlodipine prevented LV dilatation.

(MI) or amlodipine. Amlodipine decreased MAP, LVSP, LVEDP and CVP to $99 \pm 2$ mmHg ($P < 0.01$ to MI) and $114 \pm 3$ mmHg ($P < 0.05$ to MI), $15 \pm 1$ mmHg ($P < 0.01$ to MI) and $3 \pm 0$ mmHg ($P < 0.01$ to MI), respectively. The right ventricular weight was significantly higher than that in Control. The left ventricular weight in MI was not different from that in Control, which means that the weight increased by cardiac hypertrophy of the non-infarcted region was cancelled by scar formation of the infarcted region.

During the treatment period, two myocardial infarcted rats died; one in the non-treated and one in the amlodipine-treated group. There was, therefore, no difference in mortality during the treatment period. The number of myocardial infarct-size $< 20\%$ rats in non-treated and amlodipine treated group was one and two, respectively.

Table 2

<table>
<thead>
<tr>
<th>Doppler echocardiographic measurements in Sham-operated rats, rats with myocardial infarction, and amlodipine-treated rats</th>
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<tbody>
<tr>
<td><strong>Control (n = 7)</strong></td>
</tr>
<tr>
<td>LVDd, mm</td>
</tr>
<tr>
<td>LVDs, mm</td>
</tr>
<tr>
<td>FS, %</td>
</tr>
<tr>
<td>PW thickening, %</td>
</tr>
<tr>
<td>E velocity, cm/s</td>
</tr>
<tr>
<td>A velocity, cm/s</td>
</tr>
<tr>
<td>E/A</td>
</tr>
<tr>
<td>E deceleration, m/s²</td>
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</tbody>
</table>

$^{*} P < 0.05$, $^{* *} P < 0.01$ vs. control, $^{1} P < 0.05$, $^{2} P < 0.01$ vs. MI.
Fig. 2. Examples of the pulsed-wave Doppler spectra of the mitral inflow pattern from sham-operated (Control), myocardial-infarcted rats (MI) and myocardial-infarcted rats treated with amlodipine. Compared with Control, the mitral inflow pattern from the infarcted rat shows increased peak E wave velocity, rapid deceleration of the E wave, and decreased peak A wave. MI rats treated with amlodipine visually show a relatively normal transmitral flow pattern.

the ratio of E wave to A wave (Control: 1.6 ± 0.2, MI: 7.7 ± 1.0, P < 0.01) in MI.

3.2. Amlodipine improved these parameters

Gene expression of contractile proteins, ANP, and collagens after myocardial infarction and effects of amlodipine on these expressions.

Fig. 3. Typical autoradiograms of Northern blot analysis of the non-ischemic left ventricular mRNAs for α-myosin heavy chain (α-MHC), β-myosin heavy chain (β-MHC), α-cardiac actin, α-skeletal actin, atrial natriuretic polypeptide (ANP), collagen types I and III, and 18S ribosomal RNA at four weeks after myocardial infarction. Control: sham-operated rats; MI: myocardial-infarcted rats; Am: myocardial-infarcted rats treated with amlodipine.

Fig. 4 shows that β-MHC mRNA levels of non-infarcted LV and RV increased 2.0-fold and 1.9-fold, respectively, in rats four weeks after MI (P < 0.01). While α-MHC mRNA in the non-infarcted LV and RV decreased 0.5-fold (P < 0.01) and 0.7-fold (P < 0.05). α-Skeletal actin mRNA levels in the non-infarcted LV and RV increased 2.4-fold (P < 0.01) and 2.0-fold (P < 0.01). On
the other hand, α-cardiac actin was unchanged. ANP mRNA level at non-infarcted LV and RV increased 8.7-fold ($P < 0.01$) and 2.5-fold ($P < 0.01$). Collagen I and III mRNA levels of non-infarcted LV increased 4.0-fold ($P < 0.01$) and 7.1-fold ($P < 0.01$), respectively. The mRNA level in the RV increased 1.6-fold ($P < 0.01$) and 2.3-fold ($P < 0.01$), respectively, in MI.

The increased expression of β-MHC, α-skeletal actin, ANP, collagen I and III mRNAs in non-infarcted LV and RV, described above, was significantly suppressed by treatment with amlodipine non-infarcted LV: β-MHC 0.9-fold: $P < 0.01$, α-skeletal actin 1.6-fold: $P < 0.01$, ANP 5.4-fold: $P < 0.01$, collagen I 2.6-fold: $P < 0.01$, collagen III 3.9-fold, $P < 0.01$, RV: β-MHC 1.4-fold: $P < 0.05$, α-skeletal actin 1.3-fold: $P < 0.01$, ANP 0.7-fold: $P < 0.01$, collagen I 0.9-fold: $P < 0.01$, collagen III 1.2-fold: $P < 0.01$). Amlodipine did not alter α-cardiac actin mRNA levels during the experiments. On the other hand, depressed α-MHC was restored to a normal level by amlodipine both in non-infarcted LV and RV.

4. Discussion

The present study demonstrated (1) that amlodipine prevented the left ventricular cavity dilatation, the increased heart weight, systolic and diastolic dysfunction in myocardial infarcted rats, and (2) that it reduced the gene expression of fetal contractile protein and collagen mRNA expression in non-infarcted left and right ventricular myocards. These results suggest that amlodipine can prevent ventricular remodeling accompanied by cardiac dysfunction after myocardial infarction.

Calcium channel antagonists are theoretically effective in the prevention of left ventricular remodeling because of their actions as arteriolar dilators and anti-ischemic agents. Although all three classes of calcium channel antagonists now available, phenylalkylamines (e.g., verapamil), benzo-thiazepenes (e.g., diltiazem) and dihydropyridines (e.g., nifedipine, nimodipine, nitredipine), are effective vasodilators, none has been shown to produce a sustained improvement in symptoms in heart failure patients with predominant systolic ventricular dysfunction. Indeed, these drugs appear to worsen symptoms and may actually increase mortality in patients with systolic dysfunction [21–23]. The reason for these adverse effects of calcium channel antagonists in heart failure is unclear. It may be related to the known negative inotropic effects of these drugs, reflex neurohumoral activation, direct sympathetic nerve stimulation, activation of the renin–angiotensin system, or to a combination of these effects.

In this study, amlodipine decreased mean blood pressure, left ventricular systolic pressure, and left ventricular end-diastolic pressure. The afterload and preload reduction may contribute to prevent left ventricular remodeling after myocardial infarction. Moreover, amlodipine did not increase heart rate, which may not be deleterious to the progress of left ventricular remodeling. On the contrary, the prevention of remodeling by amlodipine may protect the worsening of hemodynamics. Amlodipine may break the vicious circle of the progressive cardiac dysfunction and worsening of hemodynamics during the left ventricular remodeling process.

The left ventricular remodeling is affected by hemodynamic failure and neurohumoral activation. Amlodipine has been reported to increase exercise time and to reduce symptoms and plasma norepinephrine concentration in heart failure [24]. In this study, we did not test the hypothesis that amlodipine would decrease the norepinephrine level and the sympathetic response to baroreflex stimula-
tion in myocardial infarcted rats. Moreover, the oxidative stress may be related to worse heart failure [25,26] and amlodipine has an antioxidant activity [27]. The prevention of the progressive cardiac dysfunction may partially be due to this effect. We presume that the effect of amlodipine on sympathetic or an oxidant activity may contribute to prevent the left ventricular remodeling after myocardial infarction.

Implicit in the physiological definition of heart failure is that it can be caused by an abnormal systolic function leading to a defect in the expulsion of blood (i.e., systolic heart failure), or by an abnormal diastolic function leading to a defect in ventricular filling (i.e., diastolic heart failure). The former is the more familiar — classic heart failure caused by an impaired inotropic state. Less familiar, but perhaps just as important, is diastolic heart failure in which the ability of the ventricle to accept blood is impaired [28,29]. Many aspects of diastolic function have been inferred from the pattern of transmitral flow velocity seen on pulsed-wave Doppler [30,31]. Increased peak E wave velocity, decreased peak A velocity (or absent A wave), and rapid E-wave deceleration were observed in our rats and amlodipine improved these parameters. Calcium antagonist, especially verapamil, have been shown to accelerate ventricular relaxation in patients with hypertrophic cardiomyopathy and have been reported to be useful in the treatment of diastolic dysfunction characteristic in this condition [32]. Amlodipine may improve diastolic dysfunction accompanied with preventing left ventricular remodeling. Moreover, diastolic dysfunction may be due to slowed or incomplete ventricular relaxation and amlodipine may improve it in non-infarcted myocardium directly.

Continued hypertrophy, inadequate for normalizing increased wall tension, activates an initially fetal program of gene expression exemplified by an increase in β-MHC and α-skeletal actin and accompanied by an increase in the expression of atrial natriuretic peptide [33–35]. β-MHC has low Ca\(^{2+}\)-ATPase activity and therefore low energy consumption [36], α-Skeletal actin is reported to have greater contractility than α-cardiac actin [37]. Myosin and actin isoform shifts improve cardiac muscle efficiency and correspond better to the new velocity of contraction. The reason that the decrease α-MHC and increase of β-MHC in the LV and RV in untreated infarcted rats is that the genes encoding MHC isoforms are regulated in an antithetical manner [34]. In addition, ANP is upregulated in the ventricle with increased work load [38], which probably contributes to the increased level of circulating peptide that in turn tends to decrease preload and afterload. Both phenotypic conversions and ventricular production of ANP may be compensative response to normalize the working conditions of the cardiac pump. However, these changes are not fully effective to prevent the transition from hypertrophy to failure. Moreover, we showed that collagen I and III gene expression increased in non-infarcted myocardium. It is reported that the collagen content increased in non-infarcted myocardium [39,40]. The increased interstitial collagen content of the myocardium probably enhances organ stiffness and results in cardiac dysfunction eventually leading to heart failure [39,41]. Amlodipine prevented the increased gene expression of phenotypic modulation, ANP and collagen I and III in both non-infarcted left and right ventricles. We only analyzed mRNA and did not examine protein level. We cannot comment on the property of myocardium. However, we presume that amlodipine can prevent the change of property of myocardium leading to cardiac dysfunction.

The right ventricular weight appears to be a useful marker of the overload hypertrophy induced in this model [4]. In the present study, we examined the gene expression of the right ventricle and the effect of amlodipine on these changes. The ventricular weight and the gene expression of fetal contractile proteins and collagen increased and amlodipine prevented the increase of right ventricular weight and changes of the expression of these genes. Structural remodeling and interstitial fibrosis occurs in the right ventricle of rats with myocardial infarction [42]. Thus, amlodipine could prevent the changes of quantity and quality of right ventricular remodeling after myocardial infarction. Amlodipine can prevent not only the left ventricular remodeling but also right ventricular remodeling after myocardial infarction.

5. Study limitations

Echocardiograms were performed in rats anesthetized with intraperitoneal ketamine HCl and xylazine. These anesthetics may affect the cardiac function. In fact, these anesthetics invoke a decreasing heart rate. The heart rate lowering effect prevents the summation of E and A waves. However, if possible, we should measure cardiac function without anesthesia in humans. In future studies it will be necessary for us to assess left ventricular size and function by using anesthesia which does not affect cardiac function. Moreover, we did not show the relationship between mRNA and protein levels. mRNA levels may not be necessarily representative of protein levels and, therefore, they cannot provide sufficient data to analyze the mechanism of the progressive cardiac dysfunction after myocardial infarction.

6. Summary

In summary, our study showed that amlodipine prevents left ventricular remodeling, including systolic and diastolic dysfunction, and abnormal fetal gene expression in myocardial infarcted rats. It follows that an intriguing possibility exists that suitable amlodipine administration to post-myocardial infarction subjects may overcome abnormal cardiac gene expression and morphological remodeling, thereby altering the natural course towards heart failure.
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