Matrix Metalloproteinase Inhibition Attenuates Early Left Ventricular Enlargement After Experimental Myocardial Infarction in Mice

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Background—Extracellular matrix synthesis and degradation contribute to the morphological changes that occur after myocardial infarction (MI).

Methods and Results—We tested the hypothesis that inhibition of matrix metalloproteinases (MMPs) attenuates left ventricular remodeling in experimental MI. Seventy-one male FVB mice that survived ligation of the left anterior coronary artery were randomized to a broad-spectrum MMP inhibitor (CP-471,474) or placebo by gavage. Echocardiographic studies were performed before randomization (within 24 hours of surgery) and 4 days later and included short-axis imaging at the midpapillary and apical levels. Infarction as defined by wall motion abnormality was achieved in 79% of the procedures (n=56), and mortality rate during the 4-day protocol was 23% (9 of 36 on treatment vs 7 of 35 on placebo; P=NS). Baseline end-diastolic and end-systolic dimensions and areas were similar (P=NS) between treated and placebo groups. At follow-up, infarcted mice allocated to MMP inhibitor had significantly smaller increases in end-systolic and end-diastolic dimensions and areas at both midpapillary and apical levels compared with infarcted mice allocated to placebo (all P<0.05). In addition, infarcted animals that received MMP inhibitor had no change in fractional shortening (−3±13%), whereas animals that received placebo had a decrease in fractional shortening (−12±12%) (P<0.05). In an analysis stratified by baseline end-diastolic area, the effects of MMP inhibition on the changes in end-systolic area and end-diastolic area were most prominent in animals that had more initial left ventricular dilatation (both P<0.05).

Conclusions—Administration of an MMP inhibitor attenuates early left ventricular dilation after experimental MI in mice. Further studies in genetically altered mice and other models will improve understanding of the role of MMPs in left ventricular remodeling. (Circulation. 1999;99:3063-3070.)

Key Words: myocardial infarction ■ metalloproteinases ■ left ventricle

The extent of initial ischemic damage as well as the subsequent effects of distending forces and the tissue healing process influence ventricular dilatation after myocardial infarction (MI). Dynamic expression and activation of matrix metalloproteinases (MMPs) may mediate many of the morphological changes that occur after MI at both infarcted and peri-infarcted regions. MMPs are members of a family of enzymes that degrade specific extracellular matrix components; the activity of MMPs is increased in both experimental MI and clinical dilated cardiomyopathy. Animal models of congestive heart failure, for example, demonstrate that the activity of MMP-1 (interstitial collagenase), MMP-2 (gelatinase A), and MMP-3 (stromelysin-1) rises as left ventricular end-diastolic dimension increases.

As extracellular matrix degradation may play an important role in left ventricular remodeling, MMP inhibition has emerged as a potential therapeutic strategy for patients at risk for development of congestive heart failure. Preliminary data suggest that administration of an MMP inhibitor may attenuate left ventricular enlargement in pacing-induced models of congestive heart failure and in spontaneous heart failure in rats. The effects of MMP inhibition in the post-MI period are incompletely defined. The present study evaluated the effects of administration of a broad-spectrum oral MMP inhibitor in early left ventricular remodeling as assessed by transthoracic echocardiography after experimental MI in mice.

Methods

Animals and Surgery

Male FVB mice, ranging in age from 8 to 12 weeks and in weight from 25 to 30 g, underwent left coronary artery ligation for the

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Figure 1. Chemical structure of MMP inhibitor CP-471,474.

production of MI. Surgical procedures have been described in detail elsewhere. Animals were anesthetized intraperitoneally with pentobarbital (25 to 30 μg/g). An endotracheal tube (polyethylene tube size 60) was introduced in the trachea. A volume-cycled rodent respirator (Harvard Co) provided positive pressure ventilation at 2 to 3 mL/cycle and a respiratory rate of 120 cycles/min. After the thoracic cavity was opened, ligation of the left anterior descending coronary artery was performed with a 7-0 silk suture, 3 to 4 mm from the tip of the left auricle.

The chest was closed with continuous 6-0 prolene suture, followed by a 4-0 polyester suture to close the skin. The animals were then extubated and kept warm by a heat lamp for 1 hour during the recovery period. Antibiotics were not given during the procedure, and no apparent infection developed in any animals. All mice were housed under identical conditions and given food and water ad libitum. The Standing Committee on Animal Research from Harvard Medical School approved the protocol.

Imaging Procedure

Echocardiographic studies were performed under light anesthesia and spontaneous respiration with the use of intraperitoneal tribromoethanol/amylene hydrate (Avertin, Aldrich) 2.5% wt/vol solution (8 mL/kg of mouse). Avertin was chosen for its negligible hemodynamic effects at this dose. An ultrasonographer experienced in rodent imaging, using commercially available equipment (Hewlett-Packard Sonos 5500; Hewlett-Packard Medical Products) and an M-mode FS, % 39

Apical measurements

ED diameter, mm 3.3±0.6 3.1±0.4 0.12
ES diameter, mm 2.3±0.5 2.2±0.5 0.40
M-mode FS, % 31±9 30±12 0.75
ED area, mm² 10.4±2 10.9±2 0.46
ES area, mm² 6.5±2 6.7±2 0.77
2D FAC, % 38±9 40±10 0.48

ED indicates end diastolic; ES, end systolic; FS, fractional shortening; FAC, fractional area change; and 2D, 2-dimensional.

TABLE 1. Baseline Echocardiographic Measurements From Infarcted Mice That Survived 4 Days

<table>
<thead>
<tr>
<th></th>
<th>MMP Inhibitor (n=20)</th>
<th>Placebo (n=20)</th>
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<tbody>
<tr>
<td>Midpapillary measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED diameter, mm</td>
<td>3.2±0.5</td>
<td>2.9±0.4</td>
<td>0.18</td>
</tr>
<tr>
<td>ES diameter, mm</td>
<td>1.9±0.5</td>
<td>1.8±0.5</td>
<td>0.36</td>
</tr>
<tr>
<td>M-mode FS, %</td>
<td>39±8</td>
<td>40±13</td>
<td>0.79</td>
</tr>
<tr>
<td>ED area, mm²</td>
<td>10.1±2</td>
<td>11.1±3</td>
<td>0.22</td>
</tr>
<tr>
<td>ES area, mm²</td>
<td>5.0±1</td>
<td>5.4±2</td>
<td>0.40</td>
</tr>
<tr>
<td>2D FAC, %</td>
<td>51±8</td>
<td>52±9</td>
<td>0.66</td>
</tr>
<tr>
<td>Apical measurements</td>
<td></td>
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</tr>
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<td>ES area, mm²</td>
<td>6.5±2</td>
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<td>0.77</td>
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<tr>
<td>2D FAC, %</td>
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<td>40±10</td>
<td>0.48</td>
</tr>
</tbody>
</table>

ED indicates end diastolic; ES, end systolic; FS, fractional shortening; FAC, fractional area change; and 2D, 2-dimensional.
achieve a 10 mg/mL solution and was administered at 120 mg/kg per dose and given twice per day. We chose to administer the first MMP inhibitor dose immediately after the first echocardiographic study (within the first 24 hours after the surgery) to avoid any potential drug effects on left ventricle remodeling parameters before day 1 imaging.

Tissue Collection
The mice were killed immediately after the last echocardiographic study (day 4); hearts were excised and the right and left ventricles separated. A transverse section 5 to 7 mm in length was obtained at the midventricular level to assure the inclusion of papillary muscle sections. Tissue sections were embedded in OCT compound (Miles) and frozen in 2-methylbutane chilled with liquid nitrogen. Tissue blocks were stored at −80°C until sectioning.

Echocardiographic Analysis
Echocardiographic analyses were performed without knowledge of the allocation to placebo or MMP inhibitor. From 2-dimensional short-axis imaging, endocardial borders from 3 consecutive cardiac cycles were traced at end-systole and end-diastole with the use of an off-line analysis system.15 Measurements were performed at the midpapillary level and within the apical third of the ventricle at the maximum 2-dimensional diameter. The end-systolic (smallest) and

Figure 3. Representative example of M-mode echocardiography from normal (A) and infarcted animals (B) 4 days after MI. These images were obtained from short-axis imaging at the midpapillary level. Normal animal has a small end-systolic left ventricular dimension. In infarcted animal, there is dilation of left ventricular cavity and decrease in systolic ventricular thickening. IVS indicates interventricular septum; PW, posterior wall; and arrowheads, endocardial borders.
end-diastolic (largest) cavity areas were determined. With the use of the end-diastolic and end-systolic areas, fractional area change was calculated at both levels as \[\frac{(end\ diastolic\ area - end\ systolic\ area)}{end\ diastolic\ area}\]. From M-mode short-axis imaging, end-diastolic diameter, end-systolic diameter, and fractional shortening were also calculated. For each measurement, 3 consecutive cardiac cycles were traced and averaged.

Because mouse transthoracic echocardiography is a relatively new technique, a reproducibility study was also undertaken in a separate group of animals to ensure that any potential differences between groups (treatment vs placebo) would not be influenced substantially by internal variability in the echocardiographic measurements. Echocardiograms were performed on 4 separate days in 3 mice, and end-systolic and end-diastolic measurements were performed in 6 consecutive beats. The intraclass correlation coefficients for the means between days were excellent between the animals (average \(\kappa=0.98\)).

Collagen Content
Myocardium collagen volume fraction was determined by quantitative morphometry of Sirius red–stained sections on a subset of 14 mice (7 receiving MMP inhibitor and 7 receiving placebo) with infarcts. Fresh-frozen sections (6 \(\mu m\)) were rinsed with distilled water and incubated with 0.1% Sirius red F3BA (Polyscience Inc) in saturated picric acid. Sections were then rinsed twice with 0.01N HCl for 1 minute and then immersed in distilled water. After dehydration with 70% ethanol for 30 seconds, sections were visualized under polarized light and photographed with the same exposure time for each section. Photographs in predefined regions (infarcted, noninfarcted, and border) in the infarcted mice were scanned and analyzed by morphometry with the use of a computer-based quantitative 24-bit Optimas 5.2 image analysis system (Optimas Co). Collagen volume fraction was calculated as the sum of all connective tissue divided by the sum of muscle areas and connective tissue in the visual field of the section. This approach predicts the proportion of myocardium occupied by fibrillar collagen and closely correlates with the hydroxyproline concentration of the tissue.

Statistical Analysis
In pilot studies, we found that some mice that underwent surgical ligation of the left anterior coronary artery did not have an apparent echocardiographic wall motion abnormality within the first 24 hours. Not surprisingly, these animals do not have increased left ventricular dimensions over the first 4 days after the procedure (data not shown). On the basis of these observations, this study was designed a priori to analyze only those animals who had wall motion abnormalities within 24 hours of the procedure. This determination was made at the time of the initial echocardiogram and without knowledge of...
allocation to drug or placebo. Animals without wall motion abnormalities were also randomized and analyzed separately.

Data are expressed as mean±1 SD. Continuous variables were compared between groups by use of the Student’s t test. The absolute difference between each echocardiographic parameter was used to compare the differences between animals allocated to placebo or MMP inhibitor at the follow-up echocardiogram. In addition, in a secondary analysis, data were stratified according to the baseline end-diastolic area (≤ or >0.11 cm²), representing the median of the distribution of the sample. A 2-tailed value of P<0.05 was considered statistically significant.

## Results

### Mortality and Baseline Measurements

Seventy-one mice that survived 24 hours after MI surgery underwent transthoracic echocardiography for baseline imaging and were randomized to active treatment with MMP inhibitor (n=36) or placebo (n=35) (Figure 2). During the follow-up period, 16 (23%) deaths occurred (9 mice receiving MMP inhibitor and 7 receiving placebo; P=NS). All mice that died were confirmed to have MI by initial echocardiography imaging and postmortem examination. Death was attributed to congestive heart failure and/or arrhythmias, except in 1 animal that died from left ventricular rupture (allocated to the MMP inhibitor group).

Baseline echocardiographic measurements from infarcted mice that died during follow-up were not different between active treatment or placebo groups (11.1±2.8 vs 11.4±3.4 mm², P=0.84, and 11.2±2.4 vs 11.4±3.9 mm², P=0.88; for end-diastolic area at midpapillary and apical levels, respectively). Similarly, baseline echocardiographic measurements from infarcted mice that completed the follow-up period were not different between treatment and placebo groups (Table 1). Figures 3 and 4 depict representative examples of M-mode tracings and 2-dimensional images from noninfarcted and infarcted mice. Dilatation of the left ventricular cavity, thinning of ventricular walls, and wall motion abnormalities occurred 4 days after surgery in the infarcted animals.

### Follow-Up Echocardiographic Measurements in Infarcted Animals

Although there was an overall significant increase in mean heart rate from baseline (day 1) to day 4 (from 50±78 to 59±61 bpm, P<0.001, respectively), both MMP inhibitor and placebo groups had similar changes in heart rate during this period (MMP inhibitor increased 105±76 bpm; placebo increased 87±91 bpm; P=0.49).

At follow-up, infarcted mice allocated to MMP inhibitor (n=20) had significantly smaller changes in end-systolic and end-diastolic dimensions and areas at both midpapillary and apical levels compared with infarcted mice allocated to placebo (n=20) (all P<0.05) (Table 2). In addition, infarcted animals receiving MMP inhibitor had no change in fractional shortening (−3±13%), whereas animals receiving placebo had a decrease in fractional shortening (−12±12%) (P<0.05). When all echocardiographic parameters were considered, there was a general trend for progressive left ventricular enlargement in the placebo cohort, whereas the animals receiving MMP inhibitor had no change in left ventricular dimensions.

Because left ventricular remodeling also may be related to the magnitude of the initial damage, we further stratified our follow-up analysis according to baseline echocardiographic measurements (Table 3). Interestingly, the protective effect of MMP inhibition was most prominent in animals that had greater degree of left ventricular dilatation at baseline (end-diastolic area >0.11 mm²). This effect was not observed in the placebo-treated mice (Figure 5).

### Collagen Analysis

Irrespective of treatment allocation, collagen fractional area was significantly greater in the infarcted segments when compared with the border and noninfarcted regions (19.7±10.1% vs 13.0±8.0% vs 10.1±5.8%, P=0.02, respectively) (Figure 6). No significant differences in collagen fractional area were noted between placebo and MMP inhibitor groups (n=10 vs 10, respectively) (Figure 6).

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**TABLE 2. Change in Echocardiographic Measurements From Day 1 to Day 4 in Infarcted Mice**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>MMP Inhibitor (n=20)</th>
<th>Placebo (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midpapillary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔED diameter, mm</td>
<td>-0.2±0.5</td>
<td>0.2±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔES diameter, mm</td>
<td>-0.3±0.4</td>
<td>0.1±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔM-mode FS, %</td>
<td>-3.1±3</td>
<td>-12.1±12</td>
<td>0.04</td>
</tr>
<tr>
<td>ΔED area, mm²</td>
<td>-0.7±2.9</td>
<td>1.3±2.4</td>
<td>0.03</td>
</tr>
<tr>
<td>ΔES area, mm²</td>
<td>-1.4±2</td>
<td>0.2±1.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Δ2D FAC, %</td>
<td>-4±10</td>
<td>-9±13</td>
<td>0.19</td>
</tr>
<tr>
<td>Apical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔED diameter, mm</td>
<td>-0.1±0.3</td>
<td>0.2±0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔES diameter, mm</td>
<td>-0.3±0.4</td>
<td>0.1±0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ΔM-mode FS, %</td>
<td>0.1±14</td>
<td>-6.1±10</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔED area, mm²</td>
<td>-0.9±2.3</td>
<td>1.1±2.4</td>
<td>0.01</td>
</tr>
<tr>
<td>ΔES area, mm²</td>
<td>-1.2±2.5</td>
<td>0.2±1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Δ2D FAC, %</td>
<td>-4±10</td>
<td>-7±17</td>
<td>0.48</td>
</tr>
</tbody>
</table>

ED indicates end diastolic; ES, end systolic; FS, fractional shortening; FAC, fractional area change; and 2D, 2-dimensional.

**TABLE 3. Change in Echocardiographic Measurements From Day 1 to Day 4 in Infarcted Mice Stratified by Baseline End-Diastolic Area**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Baseline ED Area ≤0.11 cm²</th>
<th>Baseline ED Area &gt;0.11 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMP Inhibitor</td>
<td>Placebo</td>
</tr>
<tr>
<td>Midpapillary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔED area, mm²</td>
<td>0.2±0.2</td>
<td>0.2±0.2</td>
</tr>
<tr>
<td>ΔES area, mm²</td>
<td>0.02±0.1</td>
<td>0.03±0.2</td>
</tr>
<tr>
<td>Δ2D FAC, %</td>
<td>5±15</td>
<td>5±9</td>
</tr>
<tr>
<td>Apical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔED area, mm²</td>
<td>0.01±0.2</td>
<td>0.1±0.3</td>
</tr>
<tr>
<td>ΔES area, mm²</td>
<td>-0.07±0.2</td>
<td>0.04±0.2</td>
</tr>
<tr>
<td>Δ2D FAC, %</td>
<td>9±18</td>
<td>4±10</td>
</tr>
</tbody>
</table>

ED indicates end diastolic; ES, end systolic; FS, fractional shortening; FAC, fractional area change; and 2D, 2-dimensional.

*P<0.05, †P<0.10, ‡P=0.17.
content were observed between treatment groups within the infarcted, border, and noninfarcted segments, although we observed a trend toward greater collagen fractional area in the infarcted segments in the MMP inhibitor group compared with the placebo group (Table 4).

Noninfarcted Animals
Animals with no obvious cardiac enlargement or wall motion abnormalities during the baseline echocardiogram were analyzed separately (noninfarcted group; n = 15). Echocardiographic parameters at both midpapillary and apical levels were significantly different in noninfarcted mice when compared with infarcted mice. End-diastolic area, end-systolic area, and fractional area change were, respectively, 6.6 ± 1.6 mm² versus 10.6 ± 2.5 mm² (P < 0.001), 1.7 ± 0.9 mm² versus 5.2 ± 1.7 mm² (P < 0.001), and 75 ± 10% versus 51 ± 9% (P < 0.001) when comparing noninfarcted with infarcted mice at the midpapillary level. Overall, mean differences between baseline (day 1) and follow-up (day 4) echocardiographic areas in the noninfarcted animals were ≤ 0.01 mm² (except for end-diastolic area at apical level = 0.05 mm²), indicating reproducibility of serial echocardiographic measurements in the noninfarcted animals.

Discussion
This study demonstrated that the administration of an MMP inhibitor attenuates early left ventricular enlargement after experimental MI in mice. This effect was most prominent in animals with initial baseline dilatation, suggesting that a particular benefit of MMP inhibition on ventricular remodeling in mice with more extensive damage. These effects, however, could not be explained by differences in collagen fractional area within different segments of the infarcted heart, indicating that factors other than collagen content may play a role in attenuating left ventricular enlargement.

Extracellular Matrix Remodeling
A growing body of evidence implicates extracellular matrix remodeling as a key element in left ventricular remodeling. Cleutjens et al. have demonstrated a transient increase in collagenase activity in the rat left ventricle that began 2 days after the infarction, peaked at day 7, and declined thereafter. Studies of collagen content also emphasize the importance of the balance between collagen synthesis and degradation. In a pacing-induced tachycardia model in pigs, for example, Spinale and colleagues demonstrated that increases in MMP activity and expression were concurrent with a reduction in total myocardial collagen content, left ventricular dilation, and myocyte contractile dysfunction. The expression of specific MMPs has also been explored in patients with end-stage congestive heart failure. When compared with normal controls, dilated cardiomyopathy ventricles had less interstitial collagenase (MMP-1) and a prominent increase in stromelysin (MMP-3) and gelatinase B (MMP-9) expression. These findings indicate that the regulation of MMPs varies with the type and timing of tissue insult.

The apparent similarity in collagen fractional area between animals allocated to placebo or MMP inhibitor observed in this study agrees with a recent report that evaluated the effects of MMP inhibition on dermal wound healing in rats. In that study, although collagen content of the wound did not differ between groups, there was a significant increase in wound strength in animals allocated to the MMP inhibitor. This finding indicates that factors other than absolute collagen...
content may be responsible for the beneficial effects of MMP inhibition. These factors could include the relative abundance of different types of collagen, collagen cross-linking, alignment and maturation, or changes in other components of extracellular matrix.22,23

The greater benefit of MMP inhibition observed in animals with larger baseline left ventricular dimensions concurs with findings from several studies that examined the effects of ACE inhibition on left ventricular remodeling parameters. For example, Pfeffer et al1 demonstrated that the greatest attenuation in ventricular enlargement and improvement in survival24 was observed in rats allocated to active drug treatment and at least moderately sized infarcts.

**Experimental MI in Mice**

Left ventricular remodeling occurs rapidly after experimental MI in mice.14 Cavity dimensions increase immediately after the infarction and evolve rapidly during the first week after the initial insult. We planned (a priori) a 4-day protocol to allow sufficient time to identify changes between treatment groups. Thus the present study does not address the important hypothesis that MMP inhibition could influence long-term ventricular remodeling. Similarly, this study does not preclude an additional effect if MMP inhibition were initiated at the time of coronary ligation or the effects on coronary occlusion with reperfusion.

The natural history of surgical MI in mice is incompletely understood and may not directly reflect pathophysiology in humans. In particular, both rats and mice lack interstitial collagenase (MMP-1), an MMP prominently expressed in many remodeling human tissues; instead, mice may degrade fibrillar collagen with an enzyme highly homologous to human MMP-13.25 The compound used in this study, CP-471,474, has a relatively high inhibitory constant for MMP-1. For this reason, compounds with this particular inhibitory spectrum may not be as effective in human left ventricular remodeling.

Several design characteristics from our study merit consideration. We and others26 have observed that different anesthetic protocols (drug, dose, and timing) during the echocardiographic study substantially affect left ventricular dimensions in mice. An echocardiographic assessment in normal mice using ketamine and xylazine as anesthetics, for example, reported significantly different echocardiographic values27 compared with values observed in our group of noninfarcted animals. During this study, we made every attempt to standardize our imaging protocol. Further, heart rate analysis indicated that both MMP inhibitor and placebo groups had similar changes in heart rate from day 1 to day 4. This finding suggests that the observed attenuation in left ventricular enlargement after MI could not be attributed to changes in heart rate. As the hemodynamic profile of CP-471,474 is incompletely described, the beneficial effects observed with CP-471,474 administration on left ventricular remodeling could at least in part be due to a hypothetical favorable hemodynamic profile of the drug. An alternative approach would have been to administer the MMP inhibitor before the surgery or immediately after surgery. Finally, the generalizability of our findings to other experimental models will depend on several intrinsic factors of the overall MMP inhibitory strategy, such as the MMP inhibitory spectrum from specific drugs, timing of administration, hemodynamic effects, and the specific characteristics of the remodeling processes in other species.

**Acknowledgment**

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**References**


**MMP Inhibition and Myocardial Infarction**


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