Age-related differences in postinfarct left ventricular rupture and remodeling

Yining Yang,1 Yitong Ma,1 Wei Han,1 Jun Li,1 Yang Xiang,1 Fen Liu,1 Xiang Ma,1 JianFa Zhang,1 Zhenyan Fu,1 Yi-Dan Su,2 Xiao-Jun Du,2 and Xiao-Ming Gao2

1Cardiovascular Research Institute, Xinjiang Medical University, Xinjiang, China; and 2Baker Heart Research Institute, Melbourne, Australia

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Yang Y, Ma Y, Han W, Li J, Xiang Y, Liu F, Ma X, Zhang J, Fu Z, Su YD, Du XJ, Gao XM. Age-related differences in postinfarct left ventricular rupture and remodeling. Am J Physiol Heart Circ Physiol 294: H1815–H1822, 2008. First published February 8, 2008; doi:10.1152/ajpheart.00831.2007.—Cardiac rupture is more prevalent in elderly patients with first onset of acute myocardial infarct (MI), but the mechanism remains unexplored. We investigated the differences in the incidence of cardiac rupture and early left ventricular (LV) remodeling following coronary artery ligation between old (12-mo) and young (3-mo) C57Bl/6 male mice and explored responsible mechanisms. The incidence of rupture within 1 wk after MI was significantly higher in old than in young mice (40.7 vs. 18.3%, P = 0.013) despite a similar infarct size in both age groups. Old mice dying of rupture had more severe infarct expansion than young counterparts. Echocardiography and catheterization at day 7 revealed more profound LV chamber dilatation and dysfunction as well as higher blood pressures in aged mice. At day 3 after MI immediately before the peak of rupture occurrence, we observed significantly higher content of type I and III collagen, a greater density of macrophage and neutrophil, and markedly enhanced mRNA expression of inflammatory cytokines in the infarcted myocardium in old than in young mice. Furthermore, a more dramatic increment of matrix metalloproteinase (MMP)-9 activity was found in old than in young infarcted hearts, in keeping with enhanced inflammatory response. Collectively, these results revealed that old mice had a higher risk of post-MI cardiac rupture despite a higher level of collagen content and cross-linking. Enhanced inflammatory response and subsequent increase in MMP-9 activity together with higher blood pressure are important factors responsible for the higher risk of cardiac rupture and more severe LV remodeling in the aged heart following acute MI. Inflammatory cytokines

AGING IS CONSIDERED as a major risk factor for cardiovascular diseases (13). Various age-associated changes in the cardiovascular system may lead to pathological outcomes, including cardiomyocyte death, arterial stiffening, myocardial hypertrophy, and desensitization of β-adrenergic signaling (13, 19). Acute myocardial infarction (MI) is the leading cause of heart failure and cardiac mortality. The risk and prevalence of acute MI increase progressively with aging (22). Left ventricular (LV) free-wall rupture represents one of the most fatal complications of acute MI, accounting for 5–31% of all in-hospital deaths (5, 21). Observational studies have reported that the free-wall LV rupture is more prevalent in elderly patients with first onset of acute MI, indicating older age is an important risk factor for post-MI cardiac rupture (4, 5, 22). However, this has not been confirmed by prospective clinical studies or experimental models, and the mechanism responsible for the age-related risk of cardiac rupture remains completely unknown.

Increased activity of matrix metalloproteinases (MMPs) following acute MI has been demonstrated in various species, including humans (15). Activated MMPs degrade the collagen network and subsequently result in the loss of structural support, distortion of tissue architecture, wall thinning, and infarct expansion (28). Experimental studies using genetically modified mouse models have shown that disruption of MMP-2 or MMP-9 attenuates post-MI rupture (10, 17), indicating a key role of MMPs and collagenolysis in the pathogenesis of cardiac rupture. Recently, Lindsey et al. (16) reported elevated levels of various MMPs by immunoblotting in senescent rat hearts, implying a possible mechanism for age-dependent extracellular matrix remodeling. Furthermore, clinical studies have shown that inflammatory markers such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) are not only predictors for coronary heart disease in the elderly (2) but also are closely associated with post-MI cardiac remodeling (18), suggesting an important role of inflammation in cardiovascular disease. It remains to be studied whether there is an enhanced inflammatory response and MMP activity in aged vs. young hearts following acute MI.

We hypothesize that an age-related difference in regional inflammation and MMP activity is responsible for a higher incidence of cardiac rupture in elder subjects following acute MI. The mouse MI model has been demonstrated, like in humans, to develop cardiac rupture (9), representing a unique opportunity for testing such a clinically relevant issue. Here we investigated 1) whether there is a difference between old and young mice in the occurrence of LV rupture and early LV remodeling following experimentally induced MI and 2) possible mechanisms responsible for the age-related difference in the risk of cardiac rupture.

MATERIALS AND METHODS

Animals and Surgery

Male C57Bl/6 mice, 3- and 12-mo of age with body weight of 23–31 g, were used. Animals were housed in a facility with a 12:12-h dark-light cycle and free access to standard mouse cow and water. All experimental procedures were approved by a local Animal Ethics Committee in accordance with the National Institutes of Health guidelines.

Mice were anesthetized using a mixture of ketamine, xylazine, and atropine (100, 20, and 1.2 mg/kg ip, respectively) and ventilated with a rodent ventilator (model 683; Harvard Apparatus). Under a dissecting microscope, a left thoracotomy was performed, and the left coronary artery was identified and occluded with a 7–0 silk suture, as

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Address for reprint requests and other correspondence: X.-M. Gao, Baker Heart Research Institute, P. O. Box 6492, St. Kilda Rd., Melbourne, 8008, Australia (e-mail: xiaoming.gao@baker.edu.au).

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described previously (9). Sham operation was performed similarly except for occlusion of the artery. Animals were inspected at least four times daily for 7 days.

**Echocardiography and Hemodynamic Assessment**

Transthoracic echocardiography was performed using a Hewlett-Packard Sonos 5500 ultrasound machine with a 15-MHz linear-array transducer, as described previously (6). Animals were lightly anesthetized with a half dose of the anesthetic mixture for surgery. The following parameters were measured and calculated: LV internal end-systolic and end-diastolic diameters (LVESd and LVEDd, respectively), external LV diastolic diameter (ExLVDd), posterior wall thickness at systole and diastole (PWs and PWd, respectively), and fractional shortening (FS% = [(LVEDd − LVESd)/LVEDd] × 100).

Hemodynamics were also determined in sham-operated and infarcted mice. After anesthesia (as used for echocardiography), a 1.4-Fr Millar catheter was placed in the LV through the right carotid artery. Arterial blood pressure, LV systolic pressure (LVSP), and the maximal rates of rise and fall in LV pressure (dP/dt max and dP/dt min, respectively) were recorded and analyzed with PowerLab Chart 4.1.2 software (ADInstruments). Heart rate was derived from pulse signals.

**Pathological and Histological Analyses**

Autopsy was performed on each animal either found dead within 1 wk or killed at day 7 after surgery, as described previously (9). The presence of a large amount of blood clot around the heart in the chest cavity and a perforation in the infarcted wall were taken to indicate rupture death. Animals with a large infarct, severe cardiac dilation, lung congestion, and pleural effusion were considered as suffering from heart failure. Body, heart (HW), and lung (LW) weights were obtained, and the tibial length was measured.

The LV was cut into halves and flattened to expose the endocardial surface. Images were taken using a digital camera and analyzed to quantify the surface areas of infarcted wall and entire LV wall. The infarcted area can be identified by its pale color, intramyocardial hemorrhages, and a reduction of the wall thickness from the noninfarcted myocardium. Infarct size was calculated as a percentage of an infarcted area in the entire LV (9). The extent of infarct expansion was estimated by measuring the largest endocardial circumference and the ratio of the thickness of the thinnest infarcted wall to averaged thickness of the ventricular septum from a single LV section stained with hematoxylin and eosin, as described previously (7).

**Quantification of Myocardial Collagen Content, Soluble and Insoluble Collagen, and Collagen Subtypes**

**Histological measurement.** A transverse LV section (5 μm) obtained from the equator of each heart was stained with 0.1% Picrosirius red. Interstitial collagen content in the LV was determined under ×20 lens using the ImageJ software (ImageJ 3.0 program, Health Science Center, University of Texas). Ten fields were chosen randomly from each specific region, including infarct and noninfarct regions and sham-operated heart. Fields containing blood vessels, epicardium, or endocardium were avoided. Collagen content was calculated and averaged as a percentage of the positive stained area in total selected fields.

**Analysis of collagen cross-linking.** Myocardial collagen can be fractionated into pepsin-soluble and -insoluble collagens; collagen cross-linking was determined from the ratio of insoluble to soluble collagen (12) by adaptation of previously described methods (20, 24) with minor modifications. Normal LVs were lyophilized, weighed, and pulverized. Samples were digested with 1 mg/ml pepsin in 0.5 M acetic acid for 24 h at 4°C and then centrifuged at 15,000 g for 45 min at 4°C to separate supernatants (soluble collagen) and pellets (insoluble collagen). Supernatants and pellets were dissolved in 6 M HCl at 110°C for 18–20 h. Aliquots of the filtered hydrolysates were lyophilized and resuspended in H2O and determined by spectrophotometry at 560 nm following reaction with chloramine T and Ehrlich’s reagents.

**Immunohistochemical staining for type I and III collagen.** LV sections (2 μm) from paraffin-embedded tissues were incubated with 0.3% hydrogen peroxide, 5% BSA for 15 min, and then anti-mouse monoclonal antibodies against type I and type III collagen (Boster) at a 1:100 dilution and 4°C overnight. The sections were then incubated with biotinylated secondary antibody for 20 min at 37°C followed by the streptavidin-peroxidase complexes tertiary system (Boster) according to the manufacturer’s instructions. After being incubated with dianisobenzidine tetrahydrochloride, sections were counterstained using hematoxylin, dehydrated through gradient alcohols, and mounted. Images were obtained using a video camera under a microscope with a ×40 lens, and 10–20 fields/section were chosen randomly from infarct and noninfarct regions or sham-operated heart. The content of type I or III collagen was measured and averaged as a percentage of the positive stained area in total selected fields.

**Determination of Inflammatory Response and MMPs**

**Nuclear density.** Nuclear density was counted from hematoxylin- and eosin-stained sections using the ImageJ 3.0 program. Ten fields at the infarcted border zone or sham-operated heart at day 5 after surgery were randomly selected under a ×20 lens.

**Identification of neutrophils and macrophages.** LV sections (2 μm) were incubated with 0.3% hydrogen peroxide and normal goat serum and then anti-mouse monoclonal antibody for neutrophil (Serotec) and CD68 antibody (KP1) for macrophages (Abcam, Jingmei Biotech) at a 1:100 dilution and 4°C overnight. The second antibody was applied for 45 min at 37°C and then followed by an established immunohistochemical protocol as mentioned before.

**Real-time PCR for inflammatory cytokine expression.** Total RNA was extracted from the infarcted and noninfarcted LVs using TRIzol. After reverse transcription, real-time quantitative PCR was performed in duplicate using a SYBR green kit (Invitrogen) and an ABI Prism 7700 system (Applied Biosystems). Primers were designed from a known mouse sequence or from the literature. Each reaction was designed to quantitate expression of TNFα, IL-1β, and IL-6. Results were normalized to reference gene 18S, as previously described (8).

**Gelatin zymography.** MMP-2 and MMP-9 activities in the infarcted and noninfarcted LVs were measured separately by gelatin zymography as described previously (25, 27) and with minor modifications. LVs were homogenized with a buffer containing 10 mM cacodylic acid, 0.15 mM NaCl, 20 mM ZnCl2, 1.5 mM NaN3, and 0.01% Triton X-100 (pH 5.0). Homogenates were centrifuged at 14,000 rpm at 4°C for 10 min. Equal loading was ensured by a protein concentration reading. Protein (50 μg) was loaded on a 7.5% acrylamide gel containing 0.5 mg/ml gelatin and electrophoresed at 4°C. The gel was washed in 2.5% Triton X-100, incubated in a developing buffer (50 mM Tris, pH 7.6, 5 mM CaCl2, 1 μM ZnCl2, and 0.02% Brij-35) for 16 h at 37°C, stained with 0.5% Coomassie blue, and destained in 10% acetic acid and 30% methanol for 120 min to visualize sharp bands. The gel was scanned, and densitometry levels were quantified using image analysis software (Quantity One; Bio-Rad).

**Experiment Protocols**

To study the age-related differences in the incidence of LV free-wall rupture and early remodeling during the acute phase of MI, 140 mice (70 each for 3- and 12-mo-old groups) were subjected to the left coronary artery ligation, and 20 mice (10 for each group) underwent sham operation. Echocardiography was performed at day 7 after surgery and then followed by catheterization for hemodynamic measurement. At the end, animals were killed, and hearts were collected for histological and molecular studies.

To study the age-related differences in myocardial collagen content, collagen subtypes and cross-linking, and MMP activities, another cohort of animals was subjected to left coronary artery ligation and
sham operation. At day 3 after surgery, mice were killed, and hearts were collected for histological measurement, immunohistochemical study, biochemical assay, real-time PCR, and zymography.

Statistics

Values are expressed as means ± SE or as a percentage. Parametric data were analyzed by one-way or two-way ANOVA for overall significance followed by the Newman-Keul’s multiple comparison or unpaired t-test. χ² or Fisher’s exact test was used to compare percentage. P < 0.05 was considered statistically significant.

RESULTS

Incidence of Rupture

Operative mortality within 24 h after surgery was similar between the two groups (14% for young vs. 16% for old mice). All 20 sham-operated mice and 119 mice with MI (3 mo old, n = 60, 12 mo old, n = 59) survived 24 h after surgery. During 1 to 7 days after MI, 45.8% of old and 25% of young mice died of either LV rupture or acute heart failure (Fig. 1A). A significantly higher incidence of LV rupture was observed in the old than in the young groups (Fig. 1A) despite a similar incidence of heart failure death and a comparable infarct size between the two groups (43.8 ± 1.3 vs. 41.2 ± 1.6%, P = not significant [NS]). The time window of rupture was 3–6 days after MI in both age groups (Fig. 1B). Incidence of plural effusion (24 vs. 12%), lung congestion (42 vs. 37%), and atrial thrombosis (29 vs. 14%) was not significantly different between old and young mice.

LV Remodeling and Dysfunction

The echocardiographic data from surviving mice at day 7 after MI are shown in Table 1. LV dimension and LV contractile function (FS) at baseline were similar between young and old groups. MI for 7 days markedly increased LV dimension as shown from LVEDd, LVESd, and ExLVDd in both age groups. MI for 7 days markedly increased LV dimension as compared with mice that survived to day 7, especially in old mice (Table 2). Wall thickness ratio and endocardial circumference were not different between the two groups with sham operation. At day 7, wall thickness ratio in infarcted hearts was reduced by 50 and 66%, and endocardial circumference was increased by 30 and 50%, respectively, in young and old groups (Table 2).

Infarct Expansion

For mice that either died of LV rupture or survived to day 7 after MI, infarct size was comparable between the two age groups. However, infarct size measured as a percentage of surface area of the LV was greater in mice dying of rupture than those survived to day 7, especially in old mice (Table 2). Wall thickness ratio and endocardial circumference were not different between the two groups with sham operation. At day 7, wall thickness ratio in infarcted hearts was reduced by 50 and 66%, and endocardial circumference was increased by 30 and 50%, respectively, in young and old groups (Table 2). Compared with mice that survived to day 7, ruptured hearts had a smaller wall thickness ratio and further enlarged endocardial circumference, and these changes were more evident in old mice, indicating a more severe infarct expansion.

Collagen Content and Cross-Linking

Figure 2A shows the changes of LV collagen content in young and old mice measured histologically from Picrosirius red-stained sections at 3 and 7 days after surgery. In sham-operated mice, total collagen content was 58% higher in old than in young mice (P < 0.05). Following MI, collagen content in the noninfarct region was increased by 2–3-fold in both age groups. In the infarct region, a 7- to 15-fold increase of collagen content were observed in young and old groups from 3 to 7 days after MI vs. respective sham values. There was no significant difference in collagen content between the two groups at all time points after MI.

Content of type I and III collagen in LV sections at 3 and 7 days after surgery was quantified by immunohistochemistry

Fig. 1. Percentage of total, rupture, and heart failure (HF) deaths (A) and time course of rupture events in 3- and 12-mo-old mice (B) during 1–7 days after myocardial infarction (MI). Twelve-mo-old (n = 59) mice had a significantly higher incidence of cardiac rupture vs. 3-mo-old (n = 60) mice (40.7 vs. 18.3%), and the peak time of rupture was day 4–5 after MI in 12-mo-old mice. *P < 0.05 vs. 3-mo-old group.
A 3-fold increase in both type I and III collagen was observed from respective sham values. At day 7 (Fig. 2, type I and III collagen content was detected in the two groups, minor change was seen in young mice compared with their C and B). The content of type I collagen in both infarct and noninfarct regions at day 7 was significantly higher in old mice. In the non–infarct region, both type I and III collagen was 60% higher while soluble collagen was 22% lower in old vs. young mice (both P < 0.05), resulting in the ratio of insoluble/soluble collagen being significantly higher in old than in young mice (Fig. 2D).

**Inflammatory Response**

Cell density was measured by nuclear counting in sham-operated hearts or in the infarcted border zone at 3 days after MI. In sham control hearts, there was no difference in cell density between young and old groups (1,431 ± 70 vs. 1,516 ± 80 nuclei/mm²). A markedly increased cell density was detected after MI, which was significantly greater in old than in young mice (5,804 ± 173 vs. 4,045 ± 298 nuclei/mm², P < 0.001).

Immunohistochemical study showed that densities of both neutrophils and macrophages in the border zone of infarcted hearts were 20 and 30% higher in old mice vs. young mice at day 3 after MI (both P < 0.05; Fig. 3A). Compared with neutrophils, the number of macrophages was significantly higher in both age groups.

mRNA expression of proinflammatory cytokines, TNF-α, IL-1β, and IL-6 was measured in both infarct and noninfarct myocardium from young and old mice at 3 days after MI. The levels of TNF-α, IL-1β, and IL-6 in the noninfarct myocardium tended to be higher in old than in young mice (P = NS; Fig. 3B). However, cytokines in the infarcted tissues increased markedly in both age groups with more profound increment seen in old mice (Fig. 3), in keeping with a denser inflammatory cell infiltration (Fig. 3B).

**Activation of MMP-2 and -9**

MMP-2 and MMP-9 activities were determined by zymography from infarct and noninfarct myocardium collected at 3 and 7 days after surgery. In sham-operated hearts, levels of MMP-2 and -9 were not significantly different between the two groups (Fig. 4). Following MI, MMP-2 activity in both infarct and noninfarct myocardium increased in a time-dependent manner. In the noninfarct region, both enzymes were higher in old mice, whereas only a trend was observed in young mice.
manner and was comparable between young and old groups (Fig. 4). Relative to the sham values, MMP-9 activity in the noninfarct myocardium was increased similarly at day 3 and returned to baseline levels at day 7 in both age groups. In contrast, MMP-9 activity in the infarct myocardium increased by 14-fold in old and 11-fold in young mice at day 3 ($P < 0.05$) and was comparable between the two groups at day 7 (Fig. 4).

**DISCUSSION**

Using a mouse model of MI, we studied the importance of age in the risk of cardiac rupture following MI and explored the potential mechanisms. We showed that 1) old mice had a significantly higher incidence of LV free wall rupture and infarct expansion than did young mice after MI; 2) LV remodeling and dysfunction were more severe in old than young animals; 3) old mice had a higher blood pressure and LVSP than young mice, implicating an elevated afterload and wall stress in the aged heart following MI; 4) despite the increased collagen content and cross-linking in the aged heart, higher levels of inflammatory cell infiltration, expression of proinflammatory cytokines, and MMP-9 activity were observed in old than in young infarcted hearts before the peak of rupture occurrence, suggesting a stronger inflammatory response and more profound collagenolytic activity in old mice following MI.

Compared with young mice, old mice had a higher incidence of post-MI rupture and a more severe infarct expansion, evidenced by a significant reduction in LV wall thickness ratio and a greater enlargement of endocardial circumference. Severe infarct expansion in aged mouse hearts is the most likely reason for the larger infarct size measured in old compared with young mice that died of rupture. Histological studies have revealed that infarct expansion is due to a slippage between muscle bundles and is associated with rupture of the infarcted wall (30). Post-MI LV remodeling is a progressive process involving chamber dilation, infarcted wall thinning, and compensatory hypertrophy in the noninfarcted myocardium (1). Echocardiography at day 7 after MI showed that LV dimension
was enlarged, whereas wall thickness and contractile function were reduced in both young and old groups. The absolute values of LVEDd, LVESd, and ExLVDd were significantly increased, and LV wall thickness and FS were markedly decreased in old vs. young mice, indicating a more profound LV remodeling and dysfunction following MI. In fact, the extent of LV remodeling measured at day 7 in old infarcted mice was underestimated considering that the 40% of old mice that died of rupture had the most severe infarct expansion. Clinical studies have also shown that elderly patients (>75 yr) had a worse LV dilation and dysfunction compared with a younger age group (<75 yr) at 1 wk after acute MI (14).

LV function was markedly impaired in infarcted mice, evidenced by depressed hemodynamic indexes. Surprisingly, old mice with MI had higher systolic and diastolic blood pressure than young mice, although there was no such differ-

Fig. 3. A: Representative images of immunohistochemical staining for neutrophils (Neu) and macrophages (MΦ) and the no. of positively stained cells counted (×40 objective) from 3- and 12-mo-old mice at day 3 after MI (n = 10/group). Images from sham-operated hearts were stained for macrophages as a reference. P < 0.05 vs. 3-mo-old group (*) and vs. neutrophils (#). B: mRNA expression of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 in both MI and NMI from 3-and 12-mo-old mice at day 3 after MI (n = 5/group). *P < 0.05 vs. respective NMI value. †P < 0.05.

Fig. 4. Total matrix metalloproteinase (MMP)-2 and MM-9 activity by zymography in sham-operated hearts and the infarct and noninfarct myocardium at day 3 and 7 after MI in both 3- and 12-mo-old groups. Representative zymographic bands correspond to individual bars (n = 8–10 mice/group). *P < 0.05 vs. respective sham values. †P < 0.05.
ence between the two age groups with sham operation. Clinical studies have reported that systolic hypertension after acute MI is associated with increased risk of cardiac rupture (4). Higher blood pressure represents an elevated afterload leading to an increased ventricular wall stress (23). The combination of morphological destruction of the infarcted wall and increased wall stress due to higher blood pressure and LVSP would make the LV more vulnerable to rupture. However, it remains to be determined whether a higher blood pressure in old mice is attributable to an enhanced sympathetic tone or activation of the ANG II system after MI.

The total collagen content in many tissue has been found to be augmented with aging (3). We observed a higher total and type III collagen content in old than in young mice with sham operation. Further biochemical assay revealed increased insoluble and decreased soluble collagen fractions in old mice, indicating an increase in collagen cross-linking with aging. Following MI, there was a time-dependent and comparable increase in total collagen in the noninfarcted and more dramatically in the infarct regions. The increase in collagen type I and III at the infarcted tissue was faster and more pronounced in old than in young mice, together with markedly elevated MMP-9 in old infarcted mice, suggesting a faster collagen turnover in aged hearts. We previously reported a high collagen content in a transgenic strain overexpressing MMP-9 in old infarcted mice, suggesting a faster collagen turnover in aged hearts together with markedly elevated soluble and decreased collagen fractions in old mice, indicating an increase in collagen cross-linking with aging. Following MI, there was a time-dependent and comparable increase in total collagen in the noninfarcted and more dramatically in the infarct regions. The increase in collagen type I and III at the infarcted tissue was faster and more pronounced in old than in young mice, together with markedly elevated MMP-9 in old infarcted mice, suggesting a faster collagen turnover in aged hearts. We previously reported a high collagen content in a transgenic strain overexpressing MMP-9 in old infarcted mice, suggesting a faster collagen turnover in aged hearts.

In conclusion, our study demonstrates a higher risk of cardiac rupture, more severe infarct expansion, and LV remodeling and dysfunction in old than in young mice after MI despite a higher collagen content and increased cross-linking in aged hearts. The underlying mechanism is a greater inflammatory cell infiltration in aged hearts that is associated with significantly enhanced expression of proinflammatory cytokines and elevated MMP-9 activity, implying a greater extent of matrix collagen degradation. In addition, a higher blood pressure, which may increase peripheral resistance and LV wall stress, may also contribute to a higher risk of rupture and more profound acute cardiac remodeling in aged hearts following MI.

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Present address for Y. Ma: Cardiovascular Research Institute, Xinjiang Medical University, 1 Liyushan Rd., Urumqi, Xinjiang, China, 830054 (e-mail: mtyx-xj@163.com).

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