Basic Science Reports

Early Short-Term Treatment With Doxycycline Modulates Postinfarction Left Ventricular Remodeling

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Background—Myocardial infarction (MI) is associated with early metalloproteinase (MMP) activation and extracellular matrix (ECM) degradation. We hypothesized that preserving the original ECM of the infarcted left ventricle (LV) by use of early short-term doxycycline (DOX) treatment preserves cardiac structure and function.

Methods and Results—LV morphometry and function were measured in 3 groups of rats (sham, MI, and MI+DOX). DOX (30 mg/kg per day) was given orally 48 hours before and 48 hours after MI. Rats were examined at 2 and 4 weeks after MI. By 4 weeks, DOX significantly decreased ($P<0.05$ versus MI) the heart weight to body weight ratio, myocyte cross-sectional area, and internal LV diameter, whereas it preserved anterior wall thickness within the infarct. Collagen/muscle area fraction did not change in the region of the infarct/scar. Parallel left shifts (versus MI) were observed in pressure-volume relationships of DOX MI rats at all pressures. DOX treatment also shifted passive epicardial strains within the scar area toward normal values. No differences were observed in LV end-diastolic or peak systolic pressures, peak positive or negative LV dP/dt, or isovolumic relaxation rates. Assessment of LV global MMP and MMP-2/9 activities 1 hour after MI using fluorescent probes yielded significant differences with DOX.

Conclusions—Brief, early MMP inhibition after MI yields preservation of LV structure and global as well as scar area passive function, supporting the concept that preserving the original ECM early after coronary occlusion lessens ventricular remodeling. (***Circulation***. 2003;108:1487-1492.)

Key Words: infarction ■ remodeling ■ collagen ■ metalloproteinases

Many patients who experience a myocardial infarction (MI) may undergo cardiac remodeling.[1] Post-MI remodeling can result in chamber dilatation as well as hypertrophy and fibrosis of noninfarcted myocardium. Severe degrees of cardiac remodeling are associated with increased risk for the development of heart failure.

Accompanying cardiac myocyte cell death in the setting of MI is damage to the existing extracellular matrix (ECM) of the heart, in particular to collagens.[2,3] The cardiac ECM provides structural support and integrity to the myocardium[4] and facilitates the conversion of myocyte contraction into pump function. The integrity of the original ECM is thought to play an important role in determining the extent of remodeling after MI.[5] In the present study we postulate that the preservation of ECM integrity after MI may serves to limit local and global ventricular remodeling. These changes are likely to be reflected in improved global and scar area function. It has been shown that physically restricting the heart during the development of MI attenuated remodeling and improved cardiac function. These results support the concept that preserving the original ECM reduces the degree of remodeling and improves the function of the scar region and normal myocardium.[6]

Degradation of ECM follows the activation of matrix metalloproteinases (MMPs). MMPs are a family of zinc-binding endoproteinases that are secreted as zymogens.[7] Reports have documented the time-dependent activation of MMPs after ischemia or MI. MMP activation can occur within minutes after ischemia, with significant increases occurring as early as 15 minutes and peaking 1 to 2 days after MI.[8–10] It is believed that early (<48-hour) MMP activation is associated with zymogen activation, whereas subsequent (>48-hour) increases are associated with inflammation.[8,9] Chronic inflammation is largely derived from macrophage infiltration[11] and is associated with enhanced expression and activity of MMPs.[9] Macrophages modulate wound healing, including the activation of fibroblasts and angiogenesis.[12,13] Angiogenesis is dependent on MMP activity.[14,15] Indeed, the inhibition of macrophage function in the setting of postinjury chronic inflammation can compromise wound healing.[13] The sequence described above of early events after ischemic injury suggests that early, short-term pharmacological inhibition of MMP activity (<48 hours) may preserve the original ECM matrix without compromising chronic inflammation-associated healing and scarring.

Doxycycline (DOX), a member of the tetracyclines, has been shown to attenuate MMP expression and activity.[16–19]

DOX can also inhibit a wider range of other proteases.[20] Studies indicate that DOX ameliorates ischemia/reperfusion injury in the setting of MI.[21] The purpose of this study was to examine the capacity of early short-term inhibition of MMP activity with DOX to affect scar formation and LV remodeling and to correlate these events with changes in global and scar area passive and contractile function.

Methods

Doxycycline Treatment

Male Sprague-Dawley rats (Harlan, Indianapolis, Ind) were used. DOX was administered orally in 2 doses at 30 mg/kg per day, a dose known to attain an effective in vivo inhibition of MMP activity.[19] Treatment began 48 hours before thoracotomy and continued to 36 hours after MI. LV function and morphology were examined at 2 time points. Two-week groups included sham-operated (n=7), untreated (n=5), and DOX-treated (n=7) MI rats; four-week groups included untreated (n=8) and DOX-treated (n=10) MI rats. All procedures were approved by the Institutional Animal Care and Use Committee and conform to published NIH guidelines for animal research.

Surgical Preparation

Animals were anesthetized with ketamine (100 mg/kg) and xylazine (5 mg/kg) intramuscularly, intubated, and positive-pressure ventilated with room air. A left thoracotomy was performed, the pericardium opened, the heart exposed, and the left anterior descending coronary artery occluded. The chest was closed, and animals were allowed to recover.

Hemodynamics

LV pressure was measured at 4 weeks in anesthetized, closed-chest rats using a Millar pressure transducer inserted via the carotid artery. Data were digitally recorded. Curve fitting was used to find the time constant of LV isovolumic relaxation (tau).

Pressure-Volume and Pressure-Strains

The techniques for measuring passive mechanics in the rat heart have been described.[22] Hearts were arrested through an apical injection of ice-cold hyperkalemic solution, and a balloon was placed into the LV. To measure 2D epicardial scar strains, a 3-mm-per-side triangle of 3 white titanium oxide markers was painted on the surface of the LV within the scar. A video camera recorded the position of the markers during inflation of the balloon to 30 mm Hg. LV pressure and volume data were obtained. Pressure-volume (PV) and pressure-strain relationships were determined relative to the zero-pressure state. Two-dimensional homogenous passive epicardial scar strains were computed with respect to a cardiac coordinate system (circumferential [E_{11}], longitudinal [E_{22}], and in-plane shear [E_{12}] strains). For each heart, strains were fitted to second-order polynomials as functions of volume, whereas pressure-volume curves were fitted to third-order polynomials and averaged.

LV Morphology

Two-Week Studies

After PV curve assessment, the heart was sectioned into 5 short-axis rings. The section that most clearly transversed the infarct area was selected for morphometry (internal and external LV diameters and LV anterior and septal wall thicknesses). Ventricular diameters were derived from exterior and interior LV circumferences, whereas wall thickness measurements at the center of the infarct and opposing (septal) wall were made in triplicate. The same ring section and the 2 adjacent rings were used to determine MI size by tracing the pale scar area and total tissue areas and calculating the percent infarct area in each ring section. Collagen area fractions were determined in Sirius Red–stained epicardial tangent plane scar sections.[22]

Four-Week Studies

Formalin-fixed LVs were embedded in wax and sectioned (10 μm) from the base of the LV, spanning the length of the scar. Sections that most clearly transversed the infarct region were stained with Masson's trichrome (for morphometry) or Sirius Red. Measurements included infarct size (found from the point where scar tissue begins and ends) as a percentage of the LV circumference, total infarct area within the cross section, and muscle and scar fractions within the infarct area. Myocyte cross-sectional areas were determined in the LV septum from H&E-stained sections taken perpendicular to the cell axis.

MMP Activity

To assess for the effects of DOX on post-MI MMP activity, 4 groups of rats were generated. Animals were killed 1 hour after thoracotomy. Sham-operated rats were generated with and without DOX (n=5 per group) as well as MI rats (n=10 per group). Flash-frozen ischemic or infarcted LV (excluding septum) and RV tissue was homogenized as previously described,[10] yielding a ×100 diluted sample. Fluorogenic peptides[8] were used to assess global MMP (MCA-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH$_2$; Biomol) and MMP-2/9 (MCA-Pro-Leu-Ala-Nva-DAP[DNP]-Ala-Arg-NH$_2$; Sigma) activities. Fluorescence was kinetically assessed using a microplate reader (340 excitation and 405 emission). The MMP inhibitor (MMPi) phenanthrolene was used to confirm that substrate cleavage was attributable to MMPs.

Data Analysis

Statistical analyses were performed with either a Student's *t* test or repeated-measures ANOVA. Results were considered to be statistically significant at $P \leq 0.05$.

Results

Two-Week Studies

Body and heart weights were similar for all groups after infarction. Heart weight to body weight ratios were 3.5 ± 0.1 for shams, 3.9 ± 0.2 for untreated animals, and 3.8 ± 0.3 for DOX animals. No significant differences in percent infarct sizes were observed between untreated and DOX-treated rats ($34 \pm 5\%$ versus $40 \pm 6\%$, respectively). No differences were observed in outer (10.5 ± 1.2 versus 10.6 ± 0.9 mm DOX) or inner (6.8 ± 0.6 versus 5.7 ± 0.5 mm DOX) LV diameters between untreated and DOX-treated MI rats. However, DOX treatment preserved anterior (infarct) wall thickness (1.7 ± 0.4 versus 1.2 ± 0.4 mm, $P<0.05$). DOX treatment at 2 weeks after MI was also accompanied by a significant reduction in scar collagen area fraction ($78 \pm 9\%$ versus $56 \pm 9\%$ DOX, $P<0.05$).

Figure 1A shows average pressure-volume (P-V) curves obtained in sham, control MI, and DOX-treated MI animals for the inflation portion of the loading cycle at 2 weeks after thoracotomy. DOX treatment produced a change in the P-V curve relationship closely resembling that observed in sham animals. Figure 1B compares average P-V curve slopes at 5 and 20 mm Hg for sham, control MI, and DOX-treated MI groups. MI led to increases in chamber stiffness versus that of sham animals. DOX reversed these changes in compliance.

Four-Week Studies

The Table summarizes hemodynamic and LV morphometry from MI and DOX groups. No significant differences were observed in peak LV pressure, heart rate, end-diastolic pressure, or peak positive or negative dP/dt or tau. With DOX treatment, significant decreases were observed by 4 weeks in
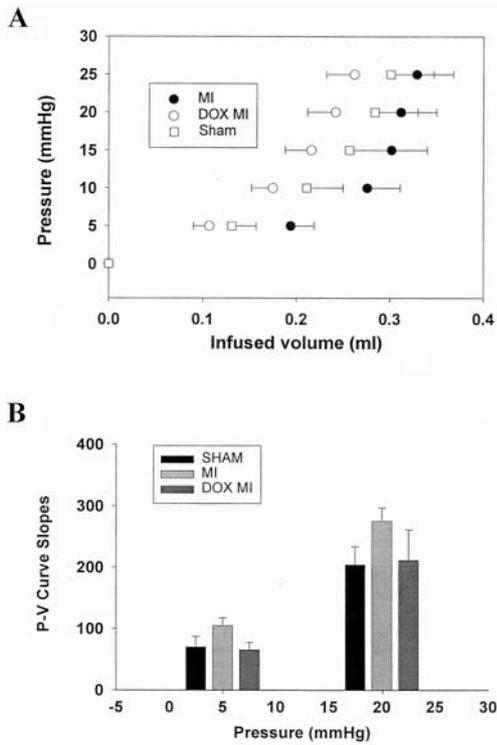
Figure 1. A, Average (mean±SEM) passive LV P-V relations for sham (n=7; □), control infarcted (n=5; ●), and DOX-treated infarcted (n=7; ○) hearts after 2 weeks. B, Average slopes of LV P-V relationships for sham, control, and DOX infarcted hearts at 5 and 20 mm Hg. DOX treatment normalized slopes of the P-V curves toward sham animal values.

heart weight, heart weight to body weight ratios, internal LV diameters, and myocyte cross-sectional areas versus control MI animals. These changes were accompanied by a significant increase in anterior LV wall thickness. No significant differences were observed in collagen area fractions within the scar. Figure 2 shows average P-V curves obtained in control MI (n=8) and DOX-treated MI (n=10) animals for the inflation portion of the loading cycle. DOX treatment resulted in a significant left-shifted P-V curve (P=0.02).

To examine differences in regional tissue mechanics within the scar, 2D epicardial strains were computed as functions of pressure in the 4-week groups (Figure 3). Positive strains indicate segment lengthening. E_{11} was greater with DOX treatment, indicating more in-plane circumferential segment lengthening with load. This trend was reversed for E_{22}; DOX treatment reduced segment lengthening in this direction. A slight shift (from positive to negative) of E_{12} was also observed with DOX treatment, suggesting a change in torsion in this region of the ventricle during filling. Figure 4 illustrates the average strains observed in control MI, DOX MI, and uninfarcted ventricles at 15 mm Hg. In the normal, noninfarcted free wall, circumferential epicardial strains are greater than longitudinal strains. As expected, in both groups, MI yielded a reduction in the magnitude of epicardial strains in scarred myocardium. However, in DOX-treated animals, the epicardial strain pattern more closely resembled that of a normal LV wall ($E_{11} > E_{22}$) versus control infarcted animals ($E_{22} > E_{11}$).

Histomorphometric and Hemodynamic Data of 4-Week Infarct Studies

	MI	Doxycycline
Hemodynamic		
Subject No.	8	8
Heart rate, bpm	235±35	263±39
Peak LV pressure, mm Hg	96±24	107±25
LV end-diastolic pressure, mm Hg	7±5.5	6.8±4
tau, ms	46±23	47±21
Peak positive dP/dt, mm Hg per s	3531±1305	3208±679
Peak negative dP/dt, mm Hg per s	3019±1145	2458±557
Histomorphometric		
Subject No.	8	10
Body weight, g	370±14	379±23
Heart weight, g	1.3±0.1	1.2±0.1*
Heart weight to body weight ratio	3.6±0.4	3.2±0.2*
Outer LV diameter, mm	10.2±0.5	10±0.6
Inner LV diameter, mm	6.2±0.6	5.6±0.6*
Infarct size, %	40±7	35±14
Anterior wall thickness, mm	1.1±0.2	1.3±0.2*
Septal wall thickness, mm	2.2±0.6	2.1±0.3
Collagen area fraction, %	92±3	88±10
Myocyte cross-sectional area, μm^2	336±90	210±32*

Data are mean±SD.
*$P < 0.05$.

We also assessed the long-term effects of DOX treatment on collagen (ie, scar) and muscle tissue content (Figure 5). Infarct areas (mm^2) were 16.4±2.0 for control MI and 20.2±2.8 for DOX MI. Muscle and scar content within the infarct area were comparable for both groups (45±9% versus 48±9% for muscle and 54±9% versus 52±9% for collagen in control MI and DOX MI, respectively). Thus, DOX treatment did not alter the ratio of muscle to scar tissue. However, because of the presence of a thicker LV wall (yielding a greater infarct area in the cross sections), DOX treatment resulted in preserved areas of both muscle and scar tissues.
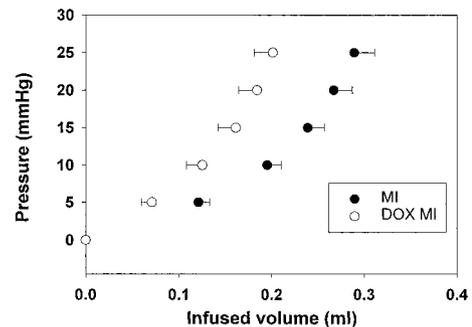

Figure 2. Average (mean±SEM) passive LV P-V relations for control infarcted (n=8; closed symbols) and DOX-treated infarcted (n=10; open symbols) hearts at 4 weeks. Two-way ANOVA indicates a significant effect of treatment on volume (P=0.04; ie, left-shifted). The interactive effect between treatment and pressure was also significant (P<0.01).
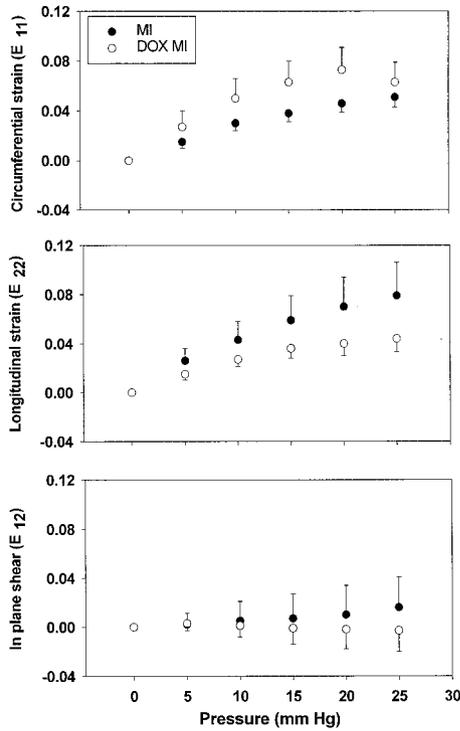
Figure 3. Two-dimensional LV epicardial strains (mean±SEM) in the infarcted (scar) area as functions of inflation pressure for animals at 4 weeks.

Figure 4. Mean (±SEM) E_{11} and E_{22} LV strains in noninfarcted, control, and DOX-treated infarcted rats at 15 mm Hg. DOX-treated rat hearts demonstrated reduced strain magnitudes reflective of a stiffer wall (scar tissue) with a pattern of deformation resembling a normal (sham) ventricular wall.

Discussion

The capacity of MMPi to preserve post-MI heart structure as well as passive and contractile function is an emerging area of research.[23,24] Wang et al[21] demonstrated using isolated perfused hearts that after 20 minutes of no-flow ischemia, there was an early increase in MMP-2 activity in the coronary effluent after reperfusion. MMP-2 release was enhanced with longer ischemia and reduced recovery of mechanical function during reperfusion. The authors noted that use of DOX improved recovery of mechanical function during reperfusion, supporting the concept that myocardial ischemia can induce activation of MMPs. In addition, their data support the idea that MMP activation is associated with induction of contractile dysfunction. Another report showed an inverse correlation between the release of MMP-2 into the coronary effluent and LV MMP activity in the setting of ischemia.[10] In this study, preconditioning of the ischemic heart preserved LV function, leading to a decreased MMP-2 release into the coronary effluent while increasing LV MMP activity by ≈18%. These results compare favorably with our observations that DOX treatment preserved LV MMP activity (16% greater versus control MI) to levels similar in shams. Furthermore, supplementation of tissue samples with DOX to levels anticipated 4 hours after treatment (35 μmol/L) yielded ≈30% inhibition in global MMP activity. Data obtained in our laboratory using pig models of MI also indicate that early short-term DOX treatment inhibits release of serum of markers of collagen degradation (unpublished observations).

Figure 6 summarizes the results observed in heart MMP activity 1 hour after thoracotomy. Global MMP activity (panel A) was significantly preserved in the ischemic or infarcted tissue in rats treated with DOX. The use of the MMP-2/9 substrate yielded comparable results. Addition of 2 mmol/L phenanthrolene to homogenates eliminated any detectable fluorescence. Supplementation of DOX (35 μmol/L) to tissue homogenates (given the ×100 dilution after homogenization) of animals treated with the drug resulted in ≈25% inhibition of MMP activity (749±60 RFU/min control versus 562±109 RFU/min DOX, $P<0.01$). Gelatin zymography experiments (data not shown) yielded only MMP-2 activity (no detectable MMP-9), indicating that the results obtained with the MMP-2/9 substrate likely reflect only MMP-2 activity.
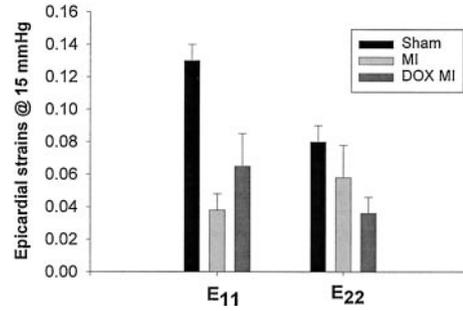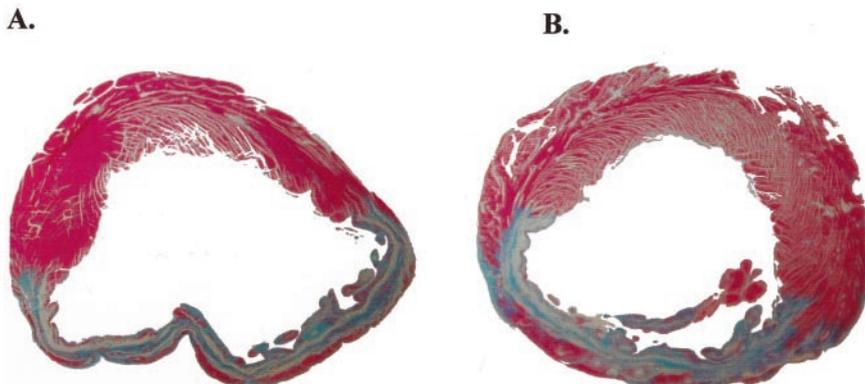

Figure 5. Representative ring sections obtained from rat hearts subjected to a 4-week MI in the absence of or with DOX treatment. Sections were stained using Masson's trichrome and visualized at low magnification (×4). Muscle tissue is seen as darker halftone, with scar tissue in light blue. Note that the thickness of the infarcted wall and the interior LV diameter of the DOX heart are preserved compared with the untreated heart.
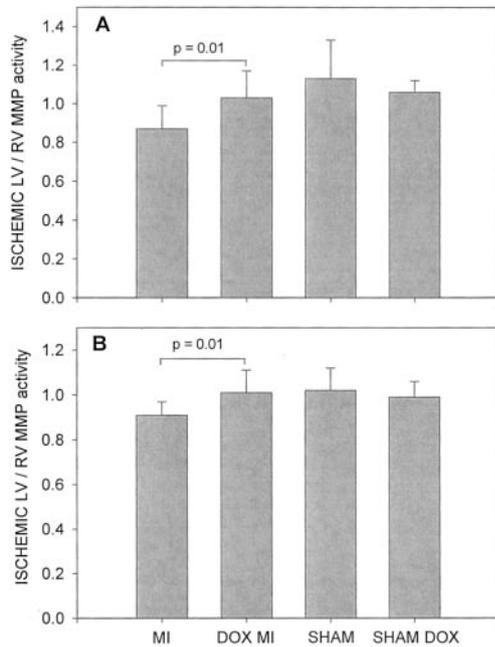
Figure 6. Global (A) and MMP-2/9 (B) activity observed in ischemic/infarcted LV tissue 2 hours after coronary occlusion in either untreated or DOX-treated sham and MI rats. MMP activity was assessed using fluorogenic substrates. LV values (RFU/min) were normalized to those of the right ventricle. Significant preservations of MMP activity were observed in ischemic and infarcted tissue of infarcted DOX rats versus those of MI controls.

Our studies in MI rats treated with DOX indicate that early in the healing/scarring phase (2 weeks), there are tendencies for reduced levels of adverse LV remodeling and improved passive function. Although thicker infarcted walls were present, collagen area fraction was reduced in the scar area, a worrisome observation if sustained over time because it may lead to compromised LV function.[15,24] Similar observations have been reported showing that continuous use of MMPi after MI in mice led to evidence of ameliorated LV remodeling in the presence of reduced scar collagen area fraction 1 week after treatment.[24] These results conflict with those of Rohde et al.[25] In this study, infarcted mice exposed to MMPi showed by day 4 after treatment greater preservation of ventricular function and reduced dilation, which was accompanied with no changes in scar collagen area fraction. In our study, however, by 4 weeks, no differences were observed in collagen area fraction between untreated and DOX-treated MI rats, indicating that tissue scarring at 2 weeks is likely incomplete.

Our results also indicate that by 4 weeks after infarction, early short-term DOX treatment attenuates ventricular remodeling as evidenced by the presence of preserved infarcted wall thickness, reduced myocyte cross-sectional areas, and decreased compensatory hypertrophy and dilatation. A recent report showed that long-term (3-week) MMPi treatment reduced LV dilatation after MI in mice. Interestingly, the authors noted that the effect was primarily attributable to differences in the first week of therapy and that no additional benefits were gained afterward.[26] Results from subsequent studies performed in rats and rabbits also support the concept that MMPi treatment in early post-MI seems to improve remodeling and function of the LV.[27] However, recent studies in which MMPi treatment was initiated 5 days after MI also demonstrated beneficial effects on LV remodeling at 2 and 8 weeks.[28] Thus, the timing of MMPi treatment remains controversial. Nonetheless, it is worth noting that long-term use of broad-spectrum MMPi in humans with MI could have unforeseen consequences, because long-term MMPi use is known to accompany adverse secondary effects.[23,24]

As noted by values shown in the Table, the contractile activity observed in the 4-week groups was somewhat low and likely reflected both the level of anesthesia and the presence of a MI. Nonetheless, results from our study indicate that by 4 weeks of DOX treatment, no significant differences in LV contractile function were observed versus untreated MI animals. The apparent lack of improvement in LV contractile function by 4 weeks may be observed at later time points (>4 weeks) after MI. Altogether, our results indicate that early short-term DOX treatment may be sufficient to realize tangible benefits in the early phases of post-MI remodeling and that the benefits gained are sustained for a reasonable period of time (4 weeks).

To investigate the possibility that muscle salvage contributes to the preservation of LV wall thickness with DOX, we examined the histological structure of 4-week infarcted hearts. Short-axis LV sections were analyzed for collagen and muscle. The increased wall thickness observed with DOX yielded a larger infarct area for this group. Our results indicate that collagen and muscle content are not different between the control MI and DOX groups. These results together with the normal myocyte cross-sectional areas observed in the septal wall (less compensatory hypertrophy) suggest that DOX treatment may attenuate the degree of infarct expansion without necessarily salvaging myocytes.

As noted above, a concern related to the use of MMPi after infarction is that it may compromise healing and scarring. With the aim of assessing the structural and functional consequences of using early short-term MMPi, we quantified changes in global and local mechanics of the LV. Results indicate that DOX treatment shifted the PV curves to the left toward the sham curves. Furthermore, the analysis of PV slopes indicated a normalization toward values observed in noninfarcted LV. Ventricular compliance tended to be normalized with DOX. These results suggest that MMPi treatment results in passive LV function that resembles "normal" tissue. MMPi treatment also yields a tendency toward the normalization of scar area strains by 4 weeks of treatment. These changes suggest that local and global passive mechanics tend to normalize with DOX.

In conclusion, early short-term treatment with DOX after infarction leads to the preservation of LV structure and passive function. Future studies are needed to examine how early MMPi treatment alters long-term passive and contractile function of infarcted hearts.

Acknowledgments

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