Ventricular remodeling in a mouse model of myocardial infarction

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The rat model of myocardial infarction (MI) has been used extensively in the study of ventricular remodeling (3, 9, 13, 17, 18, 20, 23). The mouse, however, has emerged as a powerful experimental species because of the increasing availability of transgenic strains (15), which are now becoming important in the study of cardiovascular disease (10). Therefore, characterizing an applicable model of MI in the mouse is important to examine post-MI ventricular remodeling by utilizing transgenic mice, wherein the manipulation of specific genes may allow further mechanistic insight. For example, mice expressing disrupted, nonfunctional angiotensin II type 1 (7) and angiotensin II type 2 receptors (4, 6), as well as mice that overexpress the genes encoding the β2-adrenergic receptor (14) and β-adrenergic receptor kinase (8), may provide new insights into the pathophysiology of post-MI ventricular remodeling if a mouse model of MI were available.

The objective of this study was to examine the degree to which left ventricular (LV) remodeling occurs after MI in wild-type mice and to assess the feasibility of quantifying hemodynamics and parameters of ventricular remodeling. In this study we chose a 6-wk time point utilized by some investigators in the rat MI model (20). Additionally, only a modest degree of LV dilatation was present in our preliminary studies at 2 wk.

 METHODS

Animals. Fifty-five male C57BL/6J (Charles River) mice, 8–10 wk old and 20–25 g body wt, were housed at no more than five per cage in our American Association for Accreditation of Laboratory Animal Care-approved animal facility with 12:12-h light-dark cycles and given free access to standard rodent chow (PROLAB, Syracuse, NY) and water. This protocol was approved by our Institutional Animal Research Committee.

Left coronary ligation. Mice were anesthetized using a mixture of ketamine (40 mg/kg) and pentobarbital sodium (33 mg/kg) via intraperitoneal injection. They were weighed, and the chest wall was shaved and prepared. In the supine position, endotracheal intubation was performed under direct laryngoscopy (1), and mice were ventilated with a small animal respirator (Harvard Apparatus; tidal volume = 1.0 ml, rate = 120 breaths/min). Proper intubation was confirmed by observation of chest expansion and retraction during ventilated breaths.

All surgical procedures were carried out with an operating microscope (Zeiss) at ×5 to ×24 magnification. A left thoracotomy was performed. The pectoralis muscle groups were cut transversely, exposing the thoracic cage. Occasionally, the internal mammary artery was severed, but bleeding usually stopped spontaneously or with application of pressure (with a sterile cotton swab) for ≤20 s. The fourth intercostal space was entered using scissors and blunt dissection. Two 6-0 silk...
sutures (Ethicon) were placed around the upper and lower ribs for retraction. The thymus was retracted upward, and the left lung was collapsed using a sterile cotton swab. A brief period of extreme bradycardia was often observed during manipulation of thoracic contents. Pressure was then applied to the right thorax to displace the heart leftward. A 7-0 silk suture (Ethicon) was occasionally placed into the anterosuperior portion of the LV for upward retraction to provide better exposure. Next, a 7-0 silk suture was placed through the myocardium into the anterolateral LV wall. This area corresponds to the course of the left anterior descending artery in the mouse (12). The suture was positioned approximately midway between the apex and base. Before ligation, left coronary artery entrapment was confirmed by upward traction. The apex of the LV was observed for evidence of myocardial blanching indicating interruption in coronary flow. The suture was then tied. If the myocardium did not blanch after the first ligature, then a second ligature was placed usually more laterally until proper blanching confirming epicardial ischemia, was noted. For animals undergoing a sham operation, the ligature was placed in an identical location but not tied tightly. The lungs were reexpanded using positive pressure at end expiration. The chest cavity was closed in layers with 6-0 silk, and the animal was gradually weaned from the respirator. Once spontaneous respiration resumed, the endotracheal tube was removed, and the animal was placed under a heating lamp. The animals remained in a supervised setting until fully conscious, when they were returned to their cages and given standard chow and water ad libitum.

Echocardiography. On the same day as the terminal hemodynamic study, 6 wk after surgery, 12 sham and 11 MI mice underwent transthoracic echocardiographic evaluation. A commercially available echocardiography system (HDI 3000, ATL, Bothell, WA) was utilized with a dynamically focused 10-MHz linear array transducer using a depth setting of 1.5 cm. Animals were anesthetized with a combination of ketamine and xylazine (10 mg/kg) administered by intraperitoneal injection. Mice were then placed supine in the left lateral decubitus position, and two-dimensional images and M-mode tracings were recorded using a digital color printer (model UP-1800MD, Sony). These tracings (sweep speed = 50–100 mm/s) were recorded from the short-axis view at the high papillary muscle level. Care was taken not to apply too much pressure to the chest wall.

The M-mode tracings were printed on glossy paper by using a digital color printer (model UP-1800MD, Sony). These images were coded so that measurements were performed in a blinded fashion. LV end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), and systolic and diastolic posterior wall thickness measured echocardiographically were inserted into the above equation where appropriate.

Fractional shortening (FS) was advanced proximally into the right atrium (~10 mm). A 0.3-ml bolus of saline was administered to ensure adequate intravascular volume.

The right carotid artery was localized and ligated distally, with care taken not to entrap the vagus nerve. A small clamp was placed proximally to obstruct antegrade flow, and a transverse incision was made. A segment of flame-stretched Teflon tubing (originally 0.040 in. OD stretched to ~0.015 in. OD) was inserted and secured in place. After at least 2 min had passed to allow stabilization, systemic arterial pressure was recorded using a multichannel chart recorder (model EVR, Electronics for Medicine, PPG Biomedical Systems Division, Pleasantville, NY) interfaced with a Macintosh Powerbook (Apple) computer (model 5300CS) using the MacLab 4s computerized recording and analysis system (AD Instruments, Milford, MA). All hemodynamic tracings were recorded and analyzed on the computer.

LV pressure. The cervical incision was then extended medially, and the animal was intubated using a 22-gauge Teflon Angiocath inserted directly into the trachea via tracheotomy. The animal was ventilated using a small animal respirator, as described above. Next, a left thoracotomy was performed as described above through the intercostal space below that on which the original procedure was performed. The apex of the heart was usually visible via this approach. The LV apex was immediately punctured using a 25-gauge fluid-filled needle attached to a pressure transducer (Transpac II). Optimal tracings were obtained using a 25-gauge needle and a filter setting of 2,500 Hz. Only recordings obtained using this combination were analyzed. Carotid arterial and LV pressures were monitored simultaneously to ensure that the LV pressure was not damped. LV pressure and its first derivative (dP/dt) were recorded using the monitor and computer apparatus, as described above. With the animal still under anesthesia, euthanasia was achieved with injection of 0.3 ml of 1 N KCl via the jugular venous catheter, arresting the heart in diastole.

Wall stress calculation. LV meridian systolic and diastolic wall stress were calculated using the following formula (2)

$$\sigma = \frac{3P \times D}{h \times (1 + h/D)}$$

where P is pressure, D is chamber diameter (systolic or diastolic), and h is posterior wall thickness. Systolic and diastolic LV pressures measured during the hemodynamic study were used for “P.” LV EDD and ESD and posterior wall thickness measured echocardiographically were inserted into the above equation where appropriate.

Passive pressure-volume relations. A midline sternotomy was performed, and the heart and great vessels were isolated. A double-lumen catheter with a small balloon constructed from polyethylene plastic film ligated at its tip was inserted through the mitral valve into the LV. The balloon was constructed to accommodate at least 200 µl of saline before generating any pressure itself from distension. The LV was then emptied of its contents, and the right ventricle (RV) was incised to prevent compressive effects. The balloon was inflated to 50 µl and quickly deflated to allow unfolding of the material within the ventricle. Passive pressure-volume curves were generated by sequential injections of 2.0–4.0 µl with use of a syringe with a repeating dispenser (model PB600-1, Hamilton) attached, which delivers exactly 1.0 µl of saline with each increment. LV pressure was recorded after each injection. The volume infusion was complete when the LV pressure reached ≥40 mmHg. The heart was then excised, and the atria and great vessels were trimmed away. Next, the RV free wall was trimmed carefully away from the LV.
The LV and the RV free wall were weighed to the nearest 0.1 mg and indexed by body weight (BW, in kg). The ventricles were then immersed in 10% buffered Formalin. After 24–48 h of fixation, the LV was sectioned transversely into three equal segments from apex to base and embedded in paraffin.

From the passive pressure-volume data between 2.5 and 40 mmHg, logarithmically transformed curves were developed by plotting the natural logarithm (ln) of pressure (mmHg) vs. LV volume (ml/kg). The resulting function resulted in a linear relationship, from which the slope (constant, k) was derived by the linear regression equation

\[ \ln P = k \times V + y\text{-intercept} \]

where V is volume and P is pressure (3). LV volume at a common distending pressure (10 mmHg) was calculated from this regression equation and indexed by BW. From the calculated LV volume at 10 mmHg, volume-to-mass ratio was determined by dividing the LV volume by the measured LV mass indexed by BW.

We measured liver and lung weights in approximately one-half of the animals studied. After removal of the heart, the liver and lungs were removed, blotted dry, and immediately weighed to the nearest 0.1 mg. These values were indexed by BW.

Morphometric evaluation. Serial 5-µm sections were prepared using a standard microtome. Sections were mounted and stained with hematoxylin and eosin for determination of infarct size. Quantitative histological analyses were performed on a Power Macintosh 7100 AV computer (Apple) using the public domain, NIH Image program,1 as described elsewhere (21, 23). The image analysis system consists of a Hitachi VK-C370 color videocamera, CCTV Fujinon lens, and Olympus BX40 microscope. Infarct size was determined by the method described by Pfeffer et al. (18). Infarct length was measured along the endo- and epicardial surfaces from each of the three LV sections, and values from all three sections were summed. Total LV circumference was calculated as the sum of endo- and epicardial segment lengths from all three LV sections. Infarct size (in percent) was calculated as total infarct circumference divided by total LV circumference times 100 (18).

Statistical analysis. Values are means ± SD unless otherwise indicated. Student's two tailed t-test was used to compare data from the MI group as a whole and sham animals. \( P < 0.05 \) was considered significant. The MI group was divided by median infarct size into moderate (<40%, \( n = 11 \)) and large MIs (≥40, \( n = 11 \)). When these groups were compared with the sham group and each other, ANOVA was performed using the Bonferroni/Dunn correction for multiple-group comparisons.

RESULTS

Procedure and survival. Thirty-four mice underwent thoracotomy with left coronary ligation, of which 23 (68%) survived during the follow-up period. Of these 23 animals, 1 did not exhibit an infarction by histological examination and was therefore excluded from the analysis. The mean infarct size of the animals that survived to the time of the follow-up study was 38.6 ± 15.2% (range 14–65%). Of the 11 animals that died, 4 died immediately after the procedure (within 2 h). Four of the remaining seven deaths occurred within 6 days and were confirmed secondary to cardiac rupture by autopsy; three animals died late in the post-MI course (20, 28, and 32 days). Of these seven chronic deaths, four hearts were available for histological analysis and exhibited a mean infarct size of 54 ± 7% (range 48–64%). All 21 of the sham-operated controls survived. The mean follow-up time for the surviving sham and MI groups was 41 ± 2 days.

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1 National Institutes of Health Image Analysis Program is available from the internet by anonymous ftp from Zippy.nimh.nih.gov or on floppy disk (Part No. PB93–504868, 1995) from NTIS, 5285 Port Royal Rd., Springfield, VA 22161.
Figure 1 shows a thoracotomy in which epicardial ischemia has been induced. The ligature has been placed in the anterolateral LV wall; the myocardium beyond this suture is blanched and akinetic.

Figure 2 shows hematoxylin and eosin stains of transverse LV sections (midcavity) from a sham and an MI mouse. The sections obtained from the MI mouse (infarct size = 26%) revealed an apical infarct extending into the anterolateral wall. The interventricular septum is generally spared. These infarcts were invariably transmural and typically involved the LV apex. On occasion, the infarcts were limited in size, perhaps because of the variable course of the left anterior descending artery in mice (12), which may or may not bifurcate before reaching the apex. We have accrued histological and morphometric data in a series of mice 14 days post-MI and have observed complete infarct healing at this time point as well. From the animals that died early in the post-MI period (all secondary to LV rupture), varying degrees of coagulative necrosis were present.

Hemodynamics. Hemodynamic data were obtained for all animals, but LV dP/dt measurements were possible in only 19 sham and 12 MI mice. Our methodology has evolved during the course of this initial study; many of the early dP/dt tracings were suboptimal until the most suitable needle (25-gauge) and filter (set at 2,500 Hz) combination was determined. Only recordings using this combination of needle size and filtering were analyzed and included in these data. Figure 3 demonstrates examples of LV pressure and LV dP/dt obtained from a sham-operated and an MI mouse. The MI mouse displays a lower LV dP/dt and a higher LV end-diastolic pressure (LVEDP) than the sham-operated mouse.

Hemodynamic data are summarized in Table 1. The sham group is compared with the MI group as a whole ("all infarcts") and separated by median infarct size [moderate (<40%) and large (≥40%)]. The MI mice as a whole exhibited lower systolic (P < 0.05) and diastolic blood pressures (P < 0.05) than the sham group. LVEDP was higher in the all-infarct group (P < 0.01),
which also demonstrated lower LV peak positive and negative dP/dt (P < 0.05 for both). Coinciding with the increased LV EDP was an increase in lung weight-to-BW ratio in the whole MI group vs. the sham group (6.51 ± 1.42 vs. 5.27 ± 0.83 g/kg BW, respectively, P < 0.02). However, liver weight-to-BW ratios were similar in the sham and MI groups (47.4 ± 3.1 and 47.7 ± 6.6 g/kg, respectively, P = NS), implying the absence of RV failure in the MI animals.

When the groups were separated by median infarct size, only the large-MI group displayed a significantly greater LV EDP than the sham group (P < 0.02). Although the mean LV EDP of the moderate-MI group was only slightly lower than that of the large-MI group, it did not reach statistical significance compared with the sham group. The large- and moderate-MI groups exhibited lower peak positive LV dP/dt than the sham group, but these differences were not statistically significant. The paradoxically lower positive LV dP/dt observed in the moderate- than in the large-MI group was not statistically significant. The moderate-MI group did exhibit a significantly lower peak negative dP/dt than the sham group (P < 0.02).

Ventricular mass and volumes. Table 2 displays values for LV (including the septum) and RV mass (free wall) corrected for BW in the sham-operated and MI animals. Data for the MI group as a whole are listed in the all-infarcts column and then divided by median infarct size into moderate and large MIs. The MI mice as a whole exhibited a greater LV-to-BW ratio (P < 0.01) and RV-to-BW ratio (P < 0.02) than the sham group. Figure 4 displays graphically mean LV and RV mass indexed by BW for the sham and moderate- and large-MI groups. The moderate- and large-MI groups exhibited significantly greater LV-to-BW ratios than the sham group (P < 0.02 and P < 0.01, respectively). However, only the large-MI group exhibited a significant increase in RV-to-BW ratio (P < 0.01 vs. sham and moderate-MI groups).

LV volumes were obtained immediately postmortem via passive pressure-volume relations. Measurements could not be made in one sham-operated and one MI animal (large-MI group) because of trauma to the LV as the chest was being opened. As shown in Table 2, the mean LV volume (at a common distending pressure of 10 mmHg) was more than twofold greater in the all-infarct than in the sham group (P < 0.01). Figure 5 displays graphically the mean LV volumes for the sham and moderate- and large-MI groups. The moderate-MI group developed a greater mean LV volume than the sham group, but this difference did not reach statistical significance (P = 0.059). The large-MI group exhibited a marked increase in LV volume compared with the sham (P < 0.0001) and moderate-MI groups (P < 0.01).

Echocardiography. Two-dimensional and M-mode echocardiography were performed on a subset of sham and MI animals. Examples of short-axis images and M-mode tracings obtained from a sham-operated and a large-MI mouse are shown in Fig. 6. These examples demonstrate marked LV dilatation in the MI mouse. The echocardiographic measurements are presented in Table 3. Data for the whole MI group (n = 11) are again

Table 1. Hemodynamic data

<table>
<thead>
<tr>
<th></th>
<th>Sham (n = 21)</th>
<th>All Infarcts (n = 22)</th>
<th>Moderate MI (n = 11)</th>
<th>Large MI (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>271 ± 56</td>
<td>240 ± 49</td>
<td>244 ± 61</td>
<td>237 ± 35</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>121 ± 22</td>
<td>106 ± 25*</td>
<td>105 ± 28</td>
<td>107 ± 23</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>77 ± 12</td>
<td>67 ± 18*</td>
<td>64 ± 22</td>
<td>70 ± 12</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>7.8 ± 2.2</td>
<td>11.0 ± 4.0</td>
<td>10.8 ± 4.2</td>
<td>11.1 ± 4.1†</td>
</tr>
<tr>
<td>Peak +LV dP/dt, mmHg/s</td>
<td>4,607 ± 1,374 (19)</td>
<td>3,498 ± 933* (12)</td>
<td>3,076 ± 925 (5)</td>
<td>3,800 ± 877 (7)</td>
</tr>
<tr>
<td>Peak -LV dP/dt, mmHg/s</td>
<td>-3,116 ± 932 (19)</td>
<td>-2,236 ± 507* (12)</td>
<td>-2,063 ± 421* (5)</td>
<td>-2,362 ± 556 (7)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Moderate MI, myocardial infarct <40%; large MI, myocardial infarct ≥40%; HR, heart rate; SBP and DBP, systolic and diastolic blood pressure; LV, left ventricle; dP/dt, first derivative of pressure; LVEDP, LV end-diastolic pressure. For dP/dt values, 19 of 21 sham and 12 of 22 infarcted mice were measured, as indicated by number in parentheses. *P < 0.05, †P < 0.02, ‡P < 0.01 vs. sham.
divided by median infarct size into moderate (<40%, n = 6) and large (≥40%, n = 5) groups. The MI group as a whole demonstrated significantly greater LVEDD and LVESD along with depressed FS (all P < 0.01) than the sham group (n = 12). The moderate-MI group exhibited a modest increase in LVEDD compared with the sham group that approached statistical significance (P = 0.0289). However, the large-MI group displayed a markedly increased LVEDD compared with the sham and moderate-MI groups (P < 0.0001). The moderate-MI group had a greater LVESD than the sham group (P < 0.01). The large-MI group exhibited an increased LVESD compared with the sham and moderate-MI groups (P < 0.0001). Accordingly, FS was significantly lower in the moderate- and large-MI groups than in the sham group (P < 0.01 and P < 0.0001, respectively). The large-MI group exhibited the greatest degree of LV dysfunction by this parameter.

Using systolic and diastolic LV chamber diameters and posterior wall thickness, we utilized the pressures obtained during the hemodynamic study to calculate LV meridian wall stress. These data are also shown in Table 3. There were trends for greater diastolic wall stress in the MI group as a whole and in the moderate- and large-MI groups, but these values were not statistically significant. Systolic wall stress was increased in the MI group as a whole, but this was not statistically significant. The large-MI group, however, displayed significantly greater systolic wall stress than the sham group (P < 0.02).

To examine how these in vivo measurements correlated with postmortem determination of LV volume and infarct size, regression plots were generated for LVEDD vs. both of these parameters. LVESD correlated significantly with LV volume at a common distending pressure of 10 mmHg (r = 0.84, P < 0.0001; Fig. 7A). In the MI group (moderate and large combined), LVESD correlated significantly with infarct size (r = 0.80, P < 0.01; Fig. 7B). LV volume also correlated with infarct size (r = 0.56, P < 0.01; data not shown) but less well. None of the other parameters, including LV mass, RV mass, and hemodynamic measurements, correlated significantly with infarct size.

**DISCUSSION**

This study documents a significant degree of ventricular remodeling 6 wk after MI in the mouse. In addition, we present an approach whereby ventricular remodeling can be quantified using noninvasive and invasive methodology in vivo, in addition to postmortem examination of ventricular mass and volumes. Normal C57BL/6J mice were studied, since this strain is frequently used to develop transgenic animals. Because of the small size of the mouse heart, induction of MIs and measurement of hemodynamics are technically challenging. Many researchers have utilized ex vivo preparations to overcome some of the technical difficulties (11). Inducing MIs in mice was initially described nearly 20 years ago (24). More recently, Michael et al. (12) comprehensively described mouse coronary anatomy and methods of coronary ligation. Their study was primarily acute, investigating ischemia and reperfusion. Some of their animals were allowed to survive chronically, but no data on long-term survival, hemodynamics, or indexes of ventricular remodeling were included in their report. Hutter et al. (5) reported an in vivo study of ischemia and reperfusion. This experi-

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**Table 2. Ventricular mass and volumes**

<table>
<thead>
<tr>
<th>Infarct size, %</th>
<th>Sham (n = 21)</th>
<th>All Infarcts (n = 22)</th>
<th>Moderate MI (n = 11)</th>
<th>Large MI (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW, g</td>
<td>27.9 ± 2.2</td>
<td>28.0 ± 2.7</td>
<td>27.7 ± 2.8</td>
<td>28.2 ± 2.8</td>
</tr>
<tr>
<td>LV/BW, g/kg</td>
<td>3.01 ± 0.27</td>
<td>3.43 ± 0.48*</td>
<td>3.38 ± 0.39*</td>
<td>3.48 ± 0.57b</td>
</tr>
<tr>
<td>RV/BW, g/kg</td>
<td>0.741 ± 0.074</td>
<td>0.877 ± 0.237*</td>
<td>0.776 ± 0.096</td>
<td>0.977 ± 0.300a</td>
</tr>
<tr>
<td>LV volume at P = 10 mmHg, ml/kg</td>
<td>1.24 ± 0.29</td>
<td>2.69 ± 1.59p</td>
<td>1.19 ± 0.70d</td>
<td>1.34 ± 1.83c</td>
</tr>
</tbody>
</table>

Values are means ± SD with range in parentheses. BW, body weight; LV, left ventricle (mass); P, pressure; RV, right ventricle (mass). *P < 0.02, † P < 0.001, ‡ P = 0.059 vs. sham; § P < 0.01 vs. moderate MI.
ment, performed in mice overexpressing heat shock protein 72, was acute, and no chronic data were reported. To our knowledge, our paper is the first to describe a chronic MI model in the mouse and demonstrates the quantitative evaluation of hemodynamics and parameters of ventricular remodeling.

In the present study the MI group as a whole manifested increased LVEDP and depressed positive and negative LV dP/dt. When these data were analyzed with respect to infarct size, only the large-MI group demonstrated a significant, although modest, rise in LVEDP. Both groups exhibited trends for lower peak positive LV dP/dt than the sham group. Paradoxically, positive and negative dP/dt values were even lower in the moderate- than in the large-MI group. The reason for these findings is unclear. However, in comparing the MI groups, these values were statistically similar as a result of the small number of animals and wide confidence intervals. It is possible that greater hemodynamic derangement would have been evident if the animals were studied later in the post-MI period, allowing for the development of LV decompensation and overt heart failure in a greater number of mice.

The infarctions observed in mice were notable for extensive apical involvement observed grossly and histologically. In humans, early and late ventricular remodeling is most prevalent after a transmural anterolateral infarction (17). In our series, 6 wk after MI, animals with moderate (<40%) and large (≥40%) infarcts displayed significant increases in LV mass indexed by BW compared with sham animals. This implies substantial hypertrophy of the surviving LV myocardium. Increased RV mass was observed only in those mice with large infarcts, supporting some degree of LV failure in this group. The moderate-MI group exhibited an ~50% greater mean LV volume as determined through passive pressure-volume curves constructed immediately postmortem. The large-MI group, however, developed marked LV dilatation given the nearly threefold increase in LV volume compared with the sham animals. Collectively, these findings confirm a substantial degree of ventricular remodeling after MI in this mouse model. We chose the 6-wk time point for two reasons. First, this period of time has been used by investigators studying ventricular remodeling in rats (20). Second, our preliminary studies showed only a modest degree of LV dilatation at 2 wk. On the basis of our data, a 6-wk follow-up period should be adequate to study the effect of pharmacological and/or genetic interventions on LV dilatation in mice after MI.

We applied echocardiographic techniques to many of these mice to assess the feasibility of noninvasively assessing LV size and function. Indeed, the increase in

Fig. 5. LV volumes at a common distending pressure of 10 mmHg in sham and infarcted mice. Values are means ± SE. *P = 0.059 vs. sham; †P < 0.0001 vs. sham and P < 0.01 vs. moderate-MI group.

Fig. 6. Examples of 2-dimensional (short axis, top) and M-mode echocardiographic (bottom) images in a sham-operated (A) and an infarcted (B) mouse.
LVEDD observed in the moderate- and large-MI groups correlated well with LV volume (at a common distending pressure of 10 mmHg) determined via passive pressure-volume relations. LVEDD was modestly elevated in the moderate-MI group. The large-MI group demonstrated a markedly elevated EDD that was significant compared with the sham and moderate-MI groups. Both MI groups exhibited depressed FS; however, the large-MI group demonstrated the most severe LV dysfunction by this parameter. By combining the hemodynamic and echocardiographic data, we derived pressure-volume relations obtained immediately postmortem. A, Sham-operated animals (n = 12); ○, infarcted animals (n = 11).
result, and this approach is not successful in a large percentage of cases. Given the small size of the animals, a 2-Fr (Millar) catheter is too large to cannulate the carotid artery. Newer 1.4-Fr (Millar) catheters may make closed-chest measurement of LV hemodynamics possible in most mice.

The heart rates we observed in these mice were relatively slow (mean overall rate of 260 beats/min) compared with conscious mice (generally 400–600 beats/min). This is likely related to the use of ketamine-xylazine anesthesia, an observation reported by other investigators (22). Lower heart rates may result in a decreased LV dP/dt based on the force-frequency relationship. However, the same anesthesia was applied to all animals, making comparison of the MI and sham groups valid. In subsequent studies with this model (unpublished data) and in other murine models within our laboratory (1), using a combination of ketamine and pentobarbital, we observed heart rates in the range of 400–650 beats/min.

The wall stress calculations utilized hemodynamic measurements that were obtained on the same day as the echocardiographic studies, but at a different time. In addition, the formula assumes uniform wall thickness, which is not the case in MI animals. LV pressures measured in a closed-chest fashion may allow simultaneous imaging, improving the accuracy of these calculations.

Summary. This study documents evidence of ventricular remodeling 6 wk after MI in the mouse. We have demonstrated the feasibility of measuring hemodynamics and quantifying indexes of ventricular remodeling invasively and noninvasively in this mouse MI model. Application of this model to transgenic mice, particularly those with disruptions in angiotensin II signaling (4, 6, 7), is in progress and will allow us a novel approach to investigate the pathogenesis of post-MI ventricular remodeling.

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