Assessment of cardiac function with the pressure-volume conductance system following myocardial infarction in mice

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Shioura KM, Geenen DL, Goldspink PH. Assessment of cardiac function with the pressure-volume conductance system following myocardial infarction in mice. Am J Physiol Heart Circ Physiol 293: H2870–H2877, 2007. First published August 24, 2007; doi:10.1152/ajpheart.00585.2007.—Myocardial infarction (MI) is a major cause of heart failure (HF) with the progressive worsening of cardiac performance due to structural and functional alterations. Therefore, we studied cardiac function in adult mice following MI using the Millar pressure-volume (P-V) conductance catheter system in vivo during the later phase of compensatory remodeling and decomposition to HF. We evaluated load-dependent and -independent parameters in control and 2-, 4-, 6-, and 10-wk post-MI mice and integrated changes in function with changes in gene expression. Our results indicated a significant deterioration of cardiac function in post-MI mice over time, reflected first by systolic dysfunction, followed by a transient improvement before further decline in both systolic and diastolic function. Associated with the function and adaptive remodeling were transient changes in fetal gene and extracellular matrix gene expression. However, undermining the compensatory remodeling response was a continual decline in cardiac contractility, which promoted the transition into failure. Our study provided a scheme of integrated cardiac function and gene expression changes occurring during the adaptive and maladaptive response of the heart independent of systemic vascular properties during the transition to HF following MI in mice. P-V loop analysis was used to quantitatively evaluate the gradual deterioration in cardiac function post-MI. P-V loop analysis was found to be an appropriate method for assessment of global cardiac function under varying load-dependent and -independent conditions in the murine model with many similarities to data obtained from larger animals and humans.

gene expression; contractility

The loss of any portion of viable myocardium following myocardial infarction (MI) decreases the pumping ability of the heart, which is reflected in a deterioration of cardiac function. Postinfarction remodeling of myocardium occurs to maintain cardiac output (CO). Coupled with changes in the architecture of the left ventricle (LV) are changes in gene expression during the progression from compensatory hypertrophy to chamber dilation associated with heart failure (HF). A better understanding of the functional and molecular phenotypic changes during the transition to HF following MI could be helpful in the treatment and/or prevention of HF (3, 16). The conductance catheter approach to measure the pressure-volume (P-V) relationships has been mainly used in larger animals and humans (1, 24, 31), but recently there has been great interest in the study of smaller animals, especially mice (7, 10, 14, 41). The simultaneous measurement of LV pressure and volume is a state-of-the-art approach to assess global cardiac function directly in vivo under both load-dependent and -independent conditions (3, 6, 23, 43). Echocardiography and magnetic resonance imaging (MRI) are alternative imaging techniques. Both are reliable, noninvasive, and suitable for longitudinal evaluation of regional cardiac function based on LV thickness and morphology, but only under load-dependent conditions. Echocardiography requires postimaging interpretation to derive the parameters, whereas MRI is very expensive and not readily available. MRI has sufficient spatial resolution in plane, but it has limited longitudinal resolution (1-mm slice thickness) affecting volume calculations (6). Therefore, the microconductance catheter has become an increasingly popular method to assess global cardiac function under load-dependent and -independent conditions in vivo in genetically engineered murine models for studies of human diseases (3, 16, 27–30). However, there are limited data detailing the functional changes in post-MI mice mainly due to the technically challenging procedure of surgical ligation of the coronary artery and recording hemodynamic changes during each cardiac cycle, in such small animals with high heart rates (6, 23, 32). Despite the development of a microconductance catheter system and microsurgical techniques, it is still critical to optimize these surgical procedures to accumulate replicable functional data in post-MI mice (41).

Our goal was to evaluate functional changes during the transition to HF following MI in adult mice in vivo. We used the Millar P-V conductance catheter system and integrated the changes in cardiac function with changes in gene expression. Although there are reports of cardiac function in intact and post-MI hearts, there are no comprehensive reports of the deterioration of cardiac function in post-MI mice over time using P-V loop analyses (26, 35, 38, 39). This approach permits the integrated assessment of cardiac function in the context of systemic and neurohormonal regulation, which may be helpful in targeting specific temporal and molecular events for the design of new treatments of HF.

METHODS

The experiments were conducted in accordance with the Institutional Animal Care and Use Committee and National Institutes of Health guidelines.

Animals. Forty C57/BL6 male mice weighing 20–25 g were used. Seven were designated as control without coronary artery ligation and 33 underwent coronary artery ligation, of which 29 (88%) survived.
Three (−10%) did not develop MI based on postprocedural inspection, and an additional two mice (one control and one 4 wk post-MI), did not yield P-V loops with an end-systolic pressure (ESP) higher than 60 mmHg in the open-chest configuration, so they were excluded from final analysis. There were five experimental groups of mice: control (n = 6) and post-MI at 2 wk (n = 7), 4 wk (n = 5), 6 wk (n = 6), and 10 wk (n = 7). Mice were housed separately in cages and kept in a temperature- and humidity-controlled environment with standard chow and water given ad libitum on a 12-h:12-h light/dark cycle.

Surgical preparation. Mice were initially anesthetized with 3% isoflurane inhaled in a closed chamber and an intraperitoneal injection of etomidate (10 mg/kg). Mice were intubated and connected to a rodent ventilator with a stroke volume (SV) of 0.2–0.4 ml/min and respiration rate of 135 breaths/min. A plane of anesthesia for surgery was regulated by delivery of 1.5% isoflurane through a vaporizer with 100% oxygen. All surgical manipulations were performed under a Zeiss dissecting microscope, maintaining aseptic conditions on a heated surgical pad at 40°C.

MI. A left thoracotomy was performed, and the left main coronary artery was ligated with an 8-0 prolene suture 1 to 2 mm below the ostium as previously described (2, 26). Myocardial blanching indicated a lack of perfusion. The chest cavity was closed in three layers (intercostal muscles, pectoral muscles, and skin) with 7-0 silk sutures.

![Fig. 1. Representative left ventricular (LV) pressure-volume (P-V) loops from control (A), 2 (B), 4 (C), 6 (D), and 10 (E) wk post-myocardial infarction (post-MI) mice following thoracic vena cava (TVC) occlusion in the open-chest configuration. A characteristic right shift and decline in amplitude of the pressure signal in the P-V loops is indicative of greater LV operating volumes and decreased contractility with time post-MI. ESPVR and EDPVR, end-systolic and -diastolic P-V relationships, respectively.](http://ajpheart.physiology.org/)

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The mouse was gradually weaned off the respirator, and once spontaneous respiration was resumed, the endotracheal tube was removed and the animal placed in a cage on a heating pad until fully conscious.

P-V loop analyses. A 1.4-Fr pressure-conductance catheter (SPR-839; Millar Instruments, Houston, TX) was inserted into the right carotid artery to measure baseline arterial pressure and then fed retrograde into the LV to record baseline hemodynamics in the closed chest with the ARIA Pressure Volume Conductance System (Millar Instruments). A small incision in the diaphragm was made, and open-chest hemodynamics were recorded, followed by transient occlusion of the thoracic vena cava (TVC) to vary venous return during the recording of hemodynamics (17, 45). Subsequently, parallel conductance analyses of change in pressure rise with respect to time; \( \frac{dP}{dt} \), were performed. PAMP, preload-adjusted maximal power; HR, heart rate; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; SW, stroke work; CO, cardiac output; CI, cardiac index; \( dP/dt_{max} \), maximum first derivative of change in pressure rise with respect to time; \( dP/dt_{max} \), maximum first derivative of change in pressure fall with respect to time; Tau-Glantz, time constant of fall in ventricular pressure by Glantz method; PAMP, preload-adjusted maximal power; Tau-Glantz, time constant of fall in ventricular pressure by Glantz method; PAMP, preload-adjusted maximal power; HR, heart rate; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; SW, stroke work; CO, cardiac output; CI, cardiac index; \( dP/dt_{max} \), maximum first derivative of change in pressure rise with respect to time; \( dP/dt_{max} \), maximum first derivative of change in pressure fall with respect to time; Tau-Glantz, time constant of fall in ventricular pressure by Glantz method; PAMP, preload-adjusted maximal power; Ea, arterial elastance; TPR, total peripheral resistance. * \( P < 0.05; \) † \( P < 0.01 \) vs. control.

### Results

Overall cardiac function gradually declined in post-MI mice over the 10-wk period compared with that in control mice, which is shown in the families of P-V loops obtained during transient TVC occlusions in the open-chest configuration (Fig. 1). A characteristic continuous right shift in the P-V loops and a decline in amplitude of the pressure signal indicated a greater LV operating volume due to dilation of the chamber and a decrease in contractility with time post-MI.

Based on measurements in the right carotid artery, heart rate was unchanged but the mean arterial pressure gradually declined and was significantly depressed by 10 wk post-MI (control, 72 ± 10; 2 wk MI, 61 ± 5; 4 wk MI, 60 ± 9; 6 wk MI, 68 ± 11; and 10 wk MI, 55 ± 13 mmHg; \( P < 0.05 \) for the 10 wk MI group).

With the catheter in the LV, the load-dependent hemodynamic parameters were recorded in the closed chest (Table 1). Following an incision in the diaphragm, the load-dependent hemodynamic parameters were then recorded in the open chest after stabilization (Table 2). Data derived in the closed chest showed that by 2 wk post-MI, there was a discernible level of cardiac dysfunction, as noted by a significant decline in several of the load-dependent parameters of systolic function, such as

### Table 1. Deterioration of cardiac function in mice at 2, 4, 6, and 10 wk following MI based on P-V loop measurements collected in the closed-chest configuration

<table>
<thead>
<tr>
<th>Group Parameter</th>
<th>Control</th>
<th>2 wk Post-MI</th>
<th>4 wk Post-MI</th>
<th>6 wk Post-MI</th>
<th>10 wk Post-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>534±61</td>
<td>561±63</td>
<td>573±44</td>
<td>555±51</td>
<td>523±73</td>
</tr>
<tr>
<td>ESP, mmHg</td>
<td>88±10</td>
<td>77±14</td>
<td>83±12</td>
<td>88±14</td>
<td>85±12</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>7.1±3.9</td>
<td>8.0±4.7</td>
<td>5.7±1.8</td>
<td>6.3±2.8</td>
<td>11.3±5.5</td>
</tr>
<tr>
<td>ESV, ( \mu )l</td>
<td>58±8</td>
<td>91±2.4†</td>
<td>80±4</td>
<td>61±7</td>
<td>97±6†</td>
</tr>
<tr>
<td>EDV, ( \mu )l</td>
<td>88±14</td>
<td>109±14</td>
<td>98±16</td>
<td>78±3</td>
<td>114±25†</td>
</tr>
<tr>
<td>SV, ( \mu )l</td>
<td>30.2±3.8</td>
<td>17.9±4.3†</td>
<td>18.6±3.7†</td>
<td>17.6±6.6†</td>
<td>17.2±59†</td>
</tr>
<tr>
<td>SW, mmHg/( \mu )l</td>
<td>2,154±707</td>
<td>959±2074</td>
<td>1,091±416*</td>
<td>1,169±841*</td>
<td>1,014±581†</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>16,010±4,241</td>
<td>10,245±3,487*</td>
<td>10,679±2,177*</td>
<td>9,617±3,417*</td>
<td>8,810±2,722†</td>
</tr>
<tr>
<td>CI, 1min⁻¹·kg</td>
<td>588±151</td>
<td>379±117*</td>
<td>413±73*</td>
<td>385±161*</td>
<td>332±107†</td>
</tr>
<tr>
<td>( dP/dt_{max} ), mmHg/s</td>
<td>8,398±2,460</td>
<td>6,016±1,341</td>
<td>6,778±1,616</td>
<td>7,053±1,673</td>
<td>6,545±1,451</td>
</tr>
<tr>
<td>( dP/dt_{max} ), mmHg/l</td>
<td>−8,771±1,492</td>
<td>−5,791±1,756</td>
<td>−6,182±756</td>
<td>−6,811±1,856</td>
<td>−6,294±1,133</td>
</tr>
<tr>
<td>Tau-Glantz, ms</td>
<td>9.3±2.1</td>
<td>14.6±8.1</td>
<td>12.9±5.7</td>
<td>10.3±2.4</td>
<td>9.9±1.7</td>
</tr>
<tr>
<td>PAMP, mW/ml²</td>
<td>21.2±6.6</td>
<td>6.8±3.8†</td>
<td>10.6±5.6*</td>
<td>12.9±6.6*</td>
<td>6.3±2.4†</td>
</tr>
<tr>
<td>Ea, mmHg/( \mu )l</td>
<td>3.1±0.8</td>
<td>4.6±2.1</td>
<td>4.7±1.1</td>
<td>5.8±2.3</td>
<td>5.6±2.1</td>
</tr>
<tr>
<td>TPR, mmHg·l⁻¹·min</td>
<td>4.8±1.5</td>
<td>6.2±1.7</td>
<td>5.8±1.5</td>
<td>8.1±4.3</td>
<td>6.8±2.8</td>
</tr>
</tbody>
</table>

Values are means ± SD. MI, myocardial infarction; P-V, pressure-volume; HR, heart rate; ESP, end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SV, stroke volume; SW, stroke work; CO, cardiac output; CI, cardiac index; \( dP/dt_{max} \), maximum first derivative of change in pressure rise with respect to time; \( dP/dt_{max} \), maximum first derivative of change in pressure fall with respect to time; Tau-Glantz, time constant of fall in ventricular pressure by Glantz method; PAMP, preload-adjusted maximal power; Ea, arterial elastance; TPR, total peripheral resistance. * \( P < 0.05; \) † \( P < 0.01 \) vs. control.

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SV, stroke work (SW), CO, and preload-adjusted maximal power (PAMP). These parameters remained significantly depressed at the 4 and 6 wk post-MI and declined further by 10 wk post-MI. Cardiac index derived from CO for the body weight of the animal was significantly decreased at 2 wk post-MI and then declined further by 10 wk post-MI. Pressures and volume within the LV showed characteristic responses with a drop in end-systolic pressure (ESP) and an increase in end-diastolic pressure (EDP), end-systolic volume (ESV), and end-diastolic volume (EDV) at 2 wk post-MI. Although these changes did not reach significance (except with ESV), there was a normalization of these parameters by 4 and 6 wk post-MI, before a significant increase in the volumes noted by 10 wk post-MI indicative of chamber dilation. In comparison, the maximum derivative of change in pressure rise over time (dP/dt max) and the maximum derivative of change in pressure fall over time (dP/dt min) demonstrated a continual decline over time but without reaching statistical significance. The time constant of isovolumic relaxation (Tau-Glantz) increased in post-MI mice indicating the onset of diastolic dysfunction, but by 10 wk post-MI, the value was restored to control. Changes in arterial elastance (Ea) directly effect systolic function. Ea, an index of afterload, is the ratio of ESP and SV (25, 36). Overall, Ea was elevated at post-MI and peaked at 6 wk post-MI, suggesting a change in vascular function due to either increased peripheral resistance or gradual stiffening of the arteries. Analysis of total peripheral resistance (TPR), expressed as the mean arterial pressure over CO reflecting cumulative re-

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### Table 2. Deterioration of cardiac function in mice at 2, 4, 6, and 10 wk following MI based on P-V loop measurements collected in the open-chest configuration

<table>
<thead>
<tr>
<th>Group Parameter</th>
<th>Control</th>
<th>2 wk Post-MI</th>
<th>4 wk Post-MI</th>
<th>6 wk Post-MI</th>
<th>10 wk Post-MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>545 ± 29</td>
<td>543 ± 41</td>
<td>565 ± 49</td>
<td>532 ± 83</td>
<td>499 ± 69</td>
</tr>
<tr>
<td>ESP, mmHg</td>
<td>88 ± 10</td>
<td>77 ± 11</td>
<td>81 ± 12</td>
<td>80 ± 13</td>
<td>70 ± 15</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>5.0 ± 3.4</td>
<td>6.0 ± 4.0</td>
<td>5.0 ± 4.0</td>
<td>6.0 ± 4.0</td>
<td>5.4 ± 3.8</td>
</tr>
<tr>
<td>ESV, µl</td>
<td>48 ± 14</td>
<td>84 ± 18*</td>
<td>78 ± 15*</td>
<td>56 ± 7*</td>
<td>97 ± 29*</td>
</tr>
<tr>
<td>EDV, µl</td>
<td>72.8 ± 16</td>
<td>99 ± 19</td>
<td>96 ± 15</td>
<td>72 ± 6</td>
<td>112 ± 28*</td>
</tr>
<tr>
<td>SV, µl</td>
<td>24.6 ± 3.7</td>
<td>15.5 ± 2.7*</td>
<td>18.3 ± 4.4*</td>
<td>16.0 ± 5.4*</td>
<td>14.6 ± 5.7*</td>
</tr>
<tr>
<td>SW, mmHg/µl</td>
<td>1,753 ± 396</td>
<td>854 ± 187*</td>
<td>1,040 ± 558*</td>
<td>970 ± 575*</td>
<td>700 ± 466*</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>13,417 ± 2,153</td>
<td>8,409 ± 1,515*</td>
<td>10,278 ± 2,434*</td>
<td>8,327 ± 3,018*</td>
<td>7,189 ± 2,613*</td>
</tr>
<tr>
<td>CI, 1/min·kg</td>
<td>491 ± 41</td>
<td>317 ± 42†</td>
<td>396 ± 64</td>
<td>330 ± 133*</td>
<td>273 ± 114†</td>
</tr>
<tr>
<td>dP/dt max, mmHg/s</td>
<td>8,772 ± 1,097</td>
<td>6,259 ± 1,206*</td>
<td>6,237 ± 1,378*</td>
<td>5,504 ± 2,143*</td>
<td>4,992 ± 1,750*</td>
</tr>
<tr>
<td>dP/dt min, mmHg/s</td>
<td>−7,826 ± 723</td>
<td>−5,987 ± 1,481*</td>
<td>−6,039 ± 1,381</td>
<td>−5,509 ± 1,971</td>
<td>−4,772 ± 1,867*</td>
</tr>
<tr>
<td>Tau-Glantz, ms</td>
<td>9.2 ± 2.1</td>
<td>11.0 ± 2.1</td>
<td>11 ± 4.3</td>
<td>10.8 ± 2.6</td>
<td>11.6 ± 2.7</td>
</tr>
<tr>
<td>PAMP, mW/ml²</td>
<td>26.4 ± 11.7</td>
<td>7.2 ± 3.9†</td>
<td>11.0 ± 6.8*</td>
<td>11.8 ± 6.8*</td>
<td>4.4 ± 2.0†</td>
</tr>
<tr>
<td>E a, mmHg/µl</td>
<td>3.7 ± 0.5</td>
<td>5.2 ± 1.4</td>
<td>4.6 ± 0.7</td>
<td>5.6 ± 1.6</td>
<td>5.2 ± 1.5</td>
</tr>
<tr>
<td>TPR, mmHg·ml⁻¹·min</td>
<td>5.5 ± 1.0</td>
<td>6.9 ± 0.8</td>
<td>6.1 ± 1.6</td>
<td>9.2 ± 3.8</td>
<td>8.6 ± 3.8</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05, †P < 0.01 vs. control.

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Fig. 2. Graphic representation of load-independent parameters [ESPVR (A), maximum derivative of change of pressure rise vs. end-diastolic pressure (dP/dt max, EDV), B), time-varying elastance (Ea, C), and volume intercept (D)] derived from P-V loops during TVC occlusion in control, 2, 4, 6, and 10 wk post-MI mice. Data are means ± SE. *P < 0.05, †P < 0.01 vs. control.
sistance, showed a similar trend, indicating a diminished ability of arterioles to completely relieve pressure in the arteries during diastole post-MI.

Data obtained after a small incision in the diaphragm, but before TVC occlusion, demonstrated similar directional changes as those noted in the closed-chest configuration. Overall values obtained under these conditions were slightly lower than those recorded in the closed chest but were not statistically significant. However, the values obtained in the open-chest configuration revealed a greater level of diastolic dysfunction post-MI; this could be partially explained by the absence of negative thoracic pressure compared with the closed chest. Load-dependent systolic parameters rapidly decreased at 2 wk, continually declined, and in most cases declined further by 10 wk post-MI (Table 2). The pressures and volume within the LV showed a similar response and a trend to normalize by 6 wk post-MI, as seen in the closed-chest configuration. In contrast to the closed-chest data, the dP/dt max demonstrated a significant decline over the time course compared with that in the control. Likewise, the dP/dt min also declined and was significantly lower 10 wk post-MI. Similarly, the time constant of isovolumic relaxation (τ) increased and remained elevated in post-MI mice, indicating the presence of diastolic dysfunction.

Load-independent hemodynamic parameters, obtained during transient TVC occlusions to vary preload, were used to derive indexes of cardiac contractility and are shown in Fig. 2. The slope of the end-systolic P-V relationship [ESPVR; can be defined by the slope (Ees)] significantly declined by 2 wk post-MI and continued to decline with time following MI (Fig. 2A). Although a decline in the slope of the ESPVR suggests a decrease in contractility, the volume axis intercept of the ESPVR slope reinforces the observation that chamber wall contractility is depressed over a range of increasing volumes (Fig. 2B). Interestingly, the volume axis intercept showed evidence of normalization at 6 wk MI before a steep increase, indicating dilation of the chamber coincidental with decompensation by 10 wk post-MI. The end-diastolic P-V relationship (EDPVR) was elevated at 2 and 4 wk post-MI and then declined without reaching a significant difference (control, 0.15 ± 0.06; 2 wk post-MI).

Fig. 3. Quantification of infarct size, cardiac mass, and analysis of gene expression post-MI. A: infarct size. B: heart weight-to-body weight ratios (HW/BW). C: β-myosin heavy chain (β-MHC) isoform expression. D: atrial natriuretic peptide (ANF) expression. E and F: metalloproteinase (MMP) expression MMP-2 and MMP-9, respectively. Expression was normalized to GAPDH. Data are means ± SE. *P < 0.05, #P < 0.01 vs. control.
Preload-recruitable SW (PRSW) integrates data from the entire cardiac cycle as a linear relation between SW and EDV and reveals changes in systolic function independent of chamber geometry and \( V_p \) (6, 11). The PRSW values demonstrated deterioration in LV contractile function in post-MI mice and were reduced by \( \sim 57\% \) by 10 wk post-MI compared with control. \( dP/d_{max} \) versus EDV \((dP/d_{max}\text{EDV})\) permits an analysis of contractility independent of preload. A continual depression in contractility occurred in post-MI mice that reached statistical significance at 10 wk post-MI compared with control (Fig. 2C).

The time-varying elastance indicates the temporal course of the chamber stiffness and is defined by the proportionality between intraventricular pressure and volume. Time-varying elastance \( (E_{max}) \) decreased in post-MI mice compared with control mice and reached statistical significance by the 6 and 10 wk (Fig. 2D). Finally, cardiac contractile efficiency \( (CCE) \) was obtained based on TVC occlusions in the open chest and corrected for parallel conductance. CCE, representing heart work, significantly deteriorated in post-MI mice but improved by 6 wk compared with that in control mice (control, 85 \pm 6; 2 wk MI; 73 \pm 7; 4 wk MI, 66 \pm 7; 6 wk MI, 74 \pm 8; and 10 wk MI, 67 \pm 11; \( P < 0.05 \) for 2 and 4 wk MI; \( P < 0.01 \) for 10 wk MI).

The vascular-to-ventricular coupling ratio \( (E_a/E_{es}) \) did increase in post-MI mice and reached statistical significance by 6 and 10 wk post-MI (control, 0.35 \pm 0.16; 2 wk MI, 0.56 \pm 0.16; 4 wk MI, 0.56 \pm 0.2; 6 wk MI, 1.0 \pm 0.5; and 10 wk MI, 0.9 \pm 0.4; \( P < 0.05 \) for 6 and 10 wk MI). The increase in \( E_a/E_{es} \) indicates that the decrease in mechanical efficiency of the ventricle occurred as a result of LV dysfunction largely independent of vascular changes post-MI.

To determine whether the functional decline with time post-MI and the extent of remodeling were similar in each group, infarct size was quantified. The infarcted area, expressed as a percentage of the total LV area, showed that infarcts consistently \( >40\% \) were created at all time points (Fig. 3A). The heart weight-to-body weight ratios were measured as an index of cardiac hypertrophy. A significant increase in the ratio was seen by 2 wk post-MI and maintained throughout the 10 wk post-MI period compared with that in control mice (Fig. 3B). Gene expression analysis showed a significant increase in the \( \beta \)-MHC mRNA expression in 2 wk post-MI mice, which then declined to baseline levels by 4 and 6 wk before significantly increasing again in 10 wk post-MI mice (Fig. 3C). Expression of the other embryonic/fetal marker gene, ANF, significantly increased in 2 wk post-MI mice but also declined to baseline levels at 4 wk and then did not show any further change (Fig. 3D). Expression of the MMPs have been implicated in the extracellular matrix remodeling as part of the changes in wall structure and chamber geometry post-MI. Analysis of MMP-2 mRNA expression showed that there was an increase beginning at 2 wk MI, which reaches a statistically significant peak by 4 wk before declining to baseline levels at 6 wk post-MI. This was followed by a second increase in MMP-2 expression 10 wk post-MI that was also significantly greater than that in the control (Fig. 3E). MMP-9 expression at baseline was just within the detection range of the assay and showed a similar profile of expression as seen with MMP-2 in the post-MI hearts. Expression peaked and reached statistical significance by 4 wk post-MI before declining toward baseline levels by 6 wk post-MI. Unlike MMP-2, a second increase in expression could not be detected in the 10 wk post-MI hearts (Fig. 3F).

**DISCUSSION**

Our study evaluated changes in cardiac function during the transition to HF following MI in mice using the Millar P-V loop conductance system and integrated changes in gene expression during the remodeling of the ventricle. To our knowledge, this is the first study to characterize the systolic and diastolic functional changes during the transition to HF following MI using the P-V conduction system in mice. Our results demonstrate that P-V loop analysis is an appropriate method for the assessment of cardiac function in the murine model of myocardial infarction, whereas previous reports have focused on later time points post-MI in larger animals or transgenic models of HF (26–28, 35, 47). Our study provided useful insights into contractile changes assessed by load-dependent and -independent parameters in post-MI mice during the stable phase of remodeling and transition to HF in vivo. These changes are depicted in Fig. 4 as a schematic of the functional and molecular events occurring post-MI.

Hemodynamic data obtained in the closed chest are more physiologically relevant due to normal intrathoracic pressures. However, the hemodynamic data obtained in the closed and open chest were not significantly different in the present study (Tables 1 and 2), whereas other studies have found differences (18, 45). This may be due to less trauma and loss of blood associated with accessing the TVC through the diaphragm as opposed to opening the chest cavity to expose the TVC. In addition, our method of transient TVC occlusions seems to be more effective than other reported values with occlusion of the inferior vena cava (18, 27, 28, 31, 45). Although there was variability in some of the parameters, this could be attributed to individual responses to infarcts of over 40%, the sensitivity of MMP-2 in the post-MI hearts. Expression peaked and reached statistical significance by 4 wk post-MI before declining toward baseline levels by 6 wk post-MI. Unlike MMP-2, a second increase in expression could not be detected in the 10 wk post-MI hearts (Fig. 3F).
the microcatheter to the position in the LV, and the nonlinear electrical properties of myocardium.

Both load-dependent (SV, SW, CO, dP/dt_{max/min}, τ, and PAMP) and -independent (ESPVR, EDPRVR, PRSW, and E_{max}) P-V loop-derived major parameters indicated a gradual decrease in LV function in the post-MI mice. This is depicted by the right shift and decreased amplitude of the P-V loops, indicating that the infarcted hearts were operating over larger volumes and with declining contractility. The overall decline in LV function appeared to result from an initial significant decline in systolic function (ESP, CO, SW, dP/dt_{max}, and PAMP) occurring at 2 wk, accompanied by a gradual decline in diastolic function (dP/dt_{min}, τ), which showed significance by 10 wk post-MI. However, there were notable rebounds in the volumes that occurred at the 4 and 6 wk post-MI, before declining further by 10 wk post-MI, in both closed and open-chest configurations (Tables 1 and 2). A similar trend was also noted in PAMP. Even though it never improved to control levels, the values at the 4- and 6-wk time points were less statistically significant (P < 0.05) compared with those at the 2- and 10-wk time points (P < 0.01). This apparent improvement may be due to beneficial effects of compensatory hypertension as well as scar formation and stabilization, which have been shown to occur in rodents at 2- to 3-wk post-MI (21).

Concurrent with some of these functional changes were dynamic changes in myocyte gene expression and expression of the MMPs associated with remodeling of the extracellular matrix. Sustained activation of the fetal gene program (β-MHC and ANF) did not occur and declined during the period when volumes improved despite the presence of hypertrophy. A similar decline in expression has been previously reported in rodent models of infarction over comparable time points, but others have also shown persistent expression (11, 48). These differences may reflect the use of different detection methodologies, regional variations, and the initial size of the infarct on the extent of remodeling (30). Although some of these variables were not measured in the present study and therefore limit the degree of interpretation, the extent of functional decline we observed is consistent with data published in rat hearts with infarcts >40% (34, 37). Likewise, we report very similar biphasic MMP mRNA expression as previously reported in rats over a similar period (33). In those experiments, however, enzymatic activity was continuous, indicating that remodeling of the extracellular matrix is an ongoing active process during this period. Nevertheless, these rebounds could not be sustained, and all parameters eventually declined by 10 wk post-MI. This phase was associated with a significant decline in diastolic function and accompanied by the reexpression of β-MHC and MMP-2, suggesting a secondary remodeling, which may represent the decompensation of the LV and transition to HF.

During the cardiac cycle, the work performed by the heart is confined within boundaries defined by EDPRVR and ESPVR. Within the normal physiological range of LV systolic and diastolic pressures, ESPVR is relatively independent of preload and afterload, making it a reliable index of LV contractility. The slope of the ESPVR significantly declined by 2 wk post-MI and continued to do so over the 10-wk post-MI period. Together with the other indexes of contractility (PRSW and dP/dt_{max,EDV}), these data clearly point toward an insidious decline in contractility. Consequently, the compensatory response associated with ventricular remodeling appears to take place independently of changes in contractility. Thus the beneficial effects of hypertrophy are not attributable to factors that regulate cardiac myocyte contractility but rather those geometric changes that transmit the contractile force generated by the myocardium to the ventricular chamber. However, despite these salutary remodeling effects, contractile dysfunction underlines the compensatory response and promotes decompensation into failure. At the cellular level, the contribution of depressed cardiac myocyte contractility in the viable myocardium post-MI is poorly understood. A decrease in myocyte contractility results from the dysregulation of excitation-contraction coupling due to alterations in calcium handling, myofilament function, and/or changes in the cytoskeletal architecture, which alters the passive properties and contractile dynamics of the myocyte. Despite the activation of numerous neurohormonal compensatory mechanisms, the notion that myocyte contractility is depressed in the infarcted heart due to dysregulation of excitation-contraction coupling particularly at the level of calcium handling is supported by several studies. However, others have challenged these findings (5, 13, 15, 19, 42). Recent studies have also shown that there may also be fundamental defects in myofilament function that contribute to the systolic and diastolic dysfunction during the remodeling and transition to HF (5, 42).

Our study provided a scheme of integrated cardiac function and gene expression changes occurring during the adaptive and maladaptive response of the heart during the transition to HF following MI in mice. P-V loop analysis was used to quantitatively assess the gradual deterioration of global cardiac function, which appears to be mainly due to a decrease in systolic function despite a compensatory hypertrophic response post-MI. The systolic dysfunction was apparent before prolongation of relaxation associated with diastolic dysfunction, which became evident during the decompensated phase. Delineating these events could serve for a better understanding of cardiac dysfunction following MI and to the early detection of HF.

REFERENCES


