Left ventricular function and remodeling after myocardial infarction in aging rats

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Ray a, Thomas E., Mohamed Gaballa, Peter Anderson, and Steven Goldman. Left ventricular function and remodeling after myocardial infarction in aging rats. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2652–H2658, 1997.—Adaptations of the aging left ventricle (LV) to hemodynamic overload are functionally and structurally distinct from those of the young organism. This study describes the influence of aging on LV hemodynamics and remodeling late after myocardial infarction (MI) in Fischer 344 Brown Norway rats. In sham rats at 23 mo, LV weight, myocyte cross-sectional area (CSA), and myocardial fibrosis were increased, whereas LV dp/dt, LV relaxation, and maximal LV systolic function declined with respect to younger rats (7, 12, and 18 mo of age). Isometric myocardial function was evaluated in papillary muscles of 12- and 23-mo-old sham rats. Myocardial systolic function was decreased in older rats. To determine how aging affects LV function and remodeling after MI, rats were infarcted at 7 and 18 mo of age and were studied 5 mo later. Infarct size was similar in each group. Right ventricular weight, LV end-diastolic pressure, and volume index were increased, whereas LV dp/dt, peak cardiac index, and peak developed LV pressure declined after MI. However, there were no significant differences between young and older rats in any variable of LV systolic function or remodeling after MI. Myocyte CSA increased in younger rats after MI but was unchanged in 23-mo-old rats. After MI, myocardial fibrosis was significantly increased from baseline only in younger rats. The negative interaction of aging and MI on myocyte hypertrophy and fibrosis was highly significant. The findings indicate that baseline LV and myocardial function decline with age. In the aging rat after MI, despite limited compensatory hypertrophy and more advanced baseline myocardial fibrosis, the long-term functional and structural adaptations to MI are similar to those of the mature adult heart.

fibrosis; hypertrophy; myocardial function

IN THE AGING, NONSENESCENT heart, function and structure at the left ventricular (LV) level are preserved despite significant alterations in myocardial mechanics and morphology (11). Thus aging imposes unique conditions on cardiac adaptation to LV hemodynamic overload. The specific alterations in LV function and remodeling in aging animals with experimental pressure (5, 10, 12, 16) and volume (15) overload have been well described. These include more extensive LV remodeling and mechanical dysfunction than seen in young or mature adult rats. After hemodynamic overload, aging rats have less myocardial hypertrophy (15, 16), more fibrosis (22, 33), and greater alterations in chamber geometry (12, 15, 16). Potential mechanisms to account for the greater vulnerability of the aging heart to increased loading conditions are the attenuation of contractile reserve that has been observed in the aging heart (1, 4, 8, 9, 11) and an increase in age-related myocyte dropout. The latter has been associated with more baseline fibrosis and compensatory myocyte hypertrophy (3). Myocardial infarction (MI), the most common cause of heart failure in the United States, is accompanied by cardiac adaptations that, at the myocardial and myocyte levels, resemble those found in both pressure and volume overload. After MI in young or mature adult rats, for example, myocardial and cellular contractility is depressed and is associated with eccentric and concentric myocyte hypertrophy (7, 19, 21, 30, 32), increased passive stiffness (19, 32), and increased myofibrillar collagen (19). However, it is not known how aging influences myocardial and ventricular adaptations to MI, despite the high incidence of MI and its dominant prevalence as a cause of LV dysfunction.

This study was undertaken to define the chronic effects of MI on LV performance and remodeling in the aging rat. We hypothesized that there would be more advanced LV dysfunction and remodeling in older, infarcted rats compared with infarcted mature adult rats and that these LV alterations would be associated with less compensatory myocardial hypertrophy and excess myocardial fibrosis. To take into account the possibility that aging rats have a preserved but delayed hypertrophic response (17), hemodynamic, remodeling, and morphological variables were measured 5 mo after MI. These studies were performed in the Fischer 344 Brown Norway (F344XBN) rats, which have recently been recommended by the National Institute on Aging (NIA) for the study of changes in cardiovascular function associated with aging.

MATERIALS AND METHODS

Rat model of aging. According to an Information Notice (NIA, August, 1993), F344XBN hybrids have been selected as an alternative model to the Fischer 344 rats, based on a study by the NIA which demonstrated that F344XBN have fewer detrimental pathologies and that the onset of these detriments occurs at a later age than in other crosses studied. Because there are no previously reported investigations of the effects of aging on the cardiovascular performance of the F344XBN, we studied LV function, remodeling, and myocardial fibrosis and hypertrophy in sham-operated rats at 7, 12, 18, and 23 mo (sham-7, -12, -18, and -23, respectively) of age to determine the natural cardiovascular history of this species. In addition, papillary muscle mechanics were studied in sham-12 and sham-23 rats to define cardiac function at the myocardial level. The data from these experiments are reported separately. These time points were chosen because they represent a significant period of aging of the rat cardiovascular system, in which detectable functional and morphological adaptations have occurred at the LV and myocardial
level. These time points are not meant to reflect any one-to-one correspondence to human physiological aging.

Protocol. Rats (375–475 g) underwent coronary artery ligation using techniques similar to those described previously (19, 32). Rats without autopsy-proven MI or with MI <10% of the LV were considered sham-operated rats, whereas rats with proven transmural MI >20% of the LV were designated as MI rats. The study was performed in an American Association for Accreditation of Laboratory Animal Care accredited facility with approval from the animal use committees of the Tucson Veterans Affairs Medical Center and the University of Arizona. The rats were allowed access to their respective drinking water and standard rat chow ad libitum. All rats were housed in a single room of the animal facility with a 12:12-h light-dark cycle and independent ventilation, temperature, and humidity control.

Four groups of rats formed the main body of the analysis. Control groups consisted of sham-7 and sham-18 rats that were studied 5 mo after surgery. To determine the effects of aging on myocardial function, two additional groups of rats, age 12 and 23 mo, were studied 5 mo after sham operation. The infarct groups consisted of rats that had coronary ligation at 7 and 18 mo of age and were studied 4–5 mo later. Thus the age of all rats at the time of study was either 12 or 23 mo of age; for the purpose of data presentation, the groups of rats are designated as sham-12, sham-23, MI-12, and MI-23. Only those rats with autopsy-proven MI >20% were included in the experimental groups. LV hemodynamics, variables of LV remodeling, and quantification of myocardial fibrosis and hypertrophy were evaluated at the time of study.

Baseline hemodynamics. Rats were anesthetized with thiobutarbitol (100 mg/kg ip). A 1-mm micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted into the right carotid artery. The catheter was advanced into the aorta and then into the LV under constant pressure monitoring. The zero pressure baseline was obtained by placing the pressure sensor in 37°C saline before measurements. After a period of stabilization, LV pressures were recorded and digitized at a rate of 1,000 Hz using an IBM 486 personal computer equipped with an analog-to-digital converter and customized software. From these data, LV output and the time constant of LV relaxation (tau) were calculated, according to previously described methods (26).

LV performance during maximal loading. After completion of baseline hemodynamic measurements, LV pressure development after maximal afterload was evaluated as follows (20, 25): the animal was intubated with a 20-gauge Angiocath catheter and was ventilated with a volume-cycled respirator (Harvard Apparatus, South Natick, MA). A median sternotomy was performed, and a 2–0 silk tie was positioned around the aorta. A 2- to 3-cm piece of polyethylene tubing (1.75 mm ID) was placed over the tie and was used as an occlusion device. The aorta was occluded for 2–3 s to produce isovolumic (except for coronary flow) contractions. The peak developed LV pressure was determined by measuring the difference in peak systolic and end-diastolic pressures after five stable beats. The Millar catheter was then withdrawn, and a perivascular flow probe (Transonic Systems, Ithaca, NY) was placed just superior to the aortic valve. Further positioning of the probe was done under continuous recording of mean flow until a maximum signal amplitude was obtained. After baseline flow was recorded, cardiac output after maximal volume loading was measured (20, 25) by infusing (40 ml/kg) warmed Tyrode solution via the femoral vein until plateau aortic flow (minus coronary flow) was achieved. Aortic flow at plateau divided by body weight was designated as peak cardiac index.

Isolated papillary muscle function (myocardial function). Papillary muscle function as a function of age was assessed using previously published methods (19, 32). Two separate groups of sham-operated animals, sham-12 and sham-23, were used. After completion of screening LV hemodynamic measurements, the rats were rapidly killed by removing the heart to an oxygenated dissection bath. The LV was opened from the septum, and the noninfarcted posterior papillary muscle was dissected free from the LV wall using a dissection microscope. The ends of the muscle were grasped with spring clips and were suspended vertically from an isometric force transducer (Mettric; Gould Instruments, Cleveland, OH) in a tissue bath containing modified Krebs-Henseleit solution (in mM: 120 NaCl, 5.9 KCl, 5.5 dextrose, 25 NaHCO3, 1.2 NaH2PO4, 1.2 MgCl2, and 1.2 CaCl2). The bath was maintained at a constant temperature of 30°C and was bubbled with 95% O2-5% CO2. The muscle was allowed to equilibrate for 15 min without any electrical stimulation. The muscle was then stimulated (S44; Grass Instruments, Quincy, MA) to contract isometrically at 0.33 Hz by use of field stimulation delivered through a pair of platinum electrodes placed parallel to the muscle. Five-millisecond square-wave pulses at a voltage ~10% above the threshold were used. The muscle was allowed 60 min of equilibration while being stimulated. The muscle was stretched to the length at which maximal tension development occurred (Lmax). Muscle length was measured at Lmax with the aid of a calibrated microscope (M101 AT; Gaertner Scientific, Chicago, IL) with direct real-time video feed into an IBM AT computer. Tension was recorded on a physiological recorder (Gould Recording), and digitized data points recorded at 500 Hz were stored on line on an IBM AT computer with customized software. All measurements were normalized to papillary muscle cross-sectional area (CSA) determined at Lmax. Assuming cylindrical geometry and specific gravity of 1.05, papillary muscle CSA was calculated as

\[
CSA = \text{muscle mass} / 1.05L_{\text{max}}^2
\]

From the digitized tension signals, maximum developed tension (DT), maximum rate of tension development (+DT/dt), time to peak tension development (TPT), and maximum rate of tension fall (−dT/dt) were derived.

Isolated LV pressure-volume relationships. In those rats in which papillary muscle function was not measured and after completion of all LV hemodynamic measurements, KCl was rapidly injected into a right atrial catheter to arrest the heart in diastole. Pressure-volume data were recorded using methods described earlier (26). Briefly, the heart was rapidly removed, and the right ventricle was incised. A double-lumen catheter attached to a pressure transducer (Statham 231d; Gould) and an infusion pump (Sage 341; Orion Research, Cambridge, MA) was passed into the LV and was secured with an aortic ligature. The atrioventricular groove was identified, and a ligature was passed around the heart and was tied to isolate the left atrium from the LV. After gentle aspiration of the LV cavity to remove any residual blood and to reduce the pressure to ~5 mmHg, normal saline was infused at 1 ml/min into the suspended LV while simultaneously recording pressure. Saline was infused until the pressure increased to 40 mmHg, and volume was determined from the infusion rate. Three curves were obtained from each ventricle within 10 min of the cardiac arrest. Using previously published methods (25, 26), we evaluated maximal in vivo LV dilatation by calculating the LV end-diastolic volume index, i.e., LV volume index at the specific in vivo end-diastolic pressure of each rat. To facilitate comparisons of the pressure-volume relationship between groups, we also calculated LV diastolic volume index at a common pressure of 10.
mmHg. The combined LV chamber stiffness ($K_{c}$; calculated from a monoeXponential fit of the pressure-volume data pairs) and the ratio of LV cavity volume (at distending pressure of 10 mmHg) to wall volume ($V/V_{w}$) were calculated for each curve, averaged, and reported.

Myocardial infarct size, myocyte size, and fibrosis. After recording LV pressure-volume relations, the LV catheter was withdrawn into the aortic cuff, and the coronary arteries were perfused with buffered Formalin for 15 min. After perfusion fixation of the heart, the right ventricle and LV were weighed. Twenty-four hours later, the LV were processed for quantification of fibrosis and myocyte hypertrophy. The LV was sectioned into six equal transverse slices starting from apex to base. Two of these sections were embedded in paraffin, and sections were cut at 6-µm thickness and stained with hematoxylin and eosin, aldehyde fuchsin Gomori’s trichrome, or picrosirius red. Myocardial infarct size was determined using techniques described previously (25, 26). Briefly, the trichrome-stained transverse sections of the LV were digitized using the Universal Image-1 video image analyzer system. The LV cavity and epicardial perimeter were traced, and the arc length of the infarcted region was determined. The average of the percent MI for epicardial and endocardial perimeters was calculated to obtain the percent MI for each heart.

At the light microscopic level, quantitative analysis for volume percent connective tissue (2) was performed on sections of interventricular septum that were free from scar tissue associated with the coronary artery ligation. Tissue sections stained with picrosirius red were examined with a 540-nm filter to provide contrast of the collagen with the background. With the use of digitized images collected by the video camera, the Universal Image-1 video image analyzer was used to determine the volume percent collagen for 15–20 microscopic fields for each section of interventricular septum. The mean value was calculated for each rat.

Additional sections of interventricular septum were embedded in methacrylate plastic, sectioned at 1 µm, and stained with silver. From these sections, cardiac myocyte CSA was determined using the Universal Image-1 video image analyzer system. The mean cell CSA from 100 cells/section was determined for each rat.

Statistical analysis. All results are expressed as means ± SD. Statistical comparisons between the four groups of sham-operated rats were performed using the procedure of one-way analysis of variance (ANOVA), with Student-Newman-Keuls to test for intergroup differences. Statistical comparisons of papillary muscle mechanics between sham-12 and sham-23 rats were carried out using an unpaired t-test. Statistical comparisons between the sham-operated control and MI rats were carried out using two-way ANOVA. This analysis employed a 2 × 2 matrix in which sham/MI (yes/no) represents one dimension and age (12 and 23 mo) at time of study represents the other dimension. Intergroup differences were tested using the Student-Newman-Keuls procedure. The level of significance was taken at $P < 0.05$.

RESULTS

Rat model of aging. Data are presented in mature adult (7-mo-old) through aged (23-mo-old) rats. The data sets are presented as sham-7, sham-12, sham-18, or sham-23, indicating the age of the rat at the time of study. Significant differences imply $P < 0.05$. Table 1 shows body weights, heart chamber weights, LV-to-body weight ratio, heart rate, and LV systolic pressure. Body weight increased significantly as age increased, although the differences between sham-18 and sham-23 rats were not statistically different. LV weight increased significantly during aging; LV weight in 23-mo-old rats was significantly increased compared with all younger age groups, although there was no significant increase in right ventricular weight with age. Compared with sham-7 rats, LV-to-body weight ratio declined with age. This decrease was caused by the gradual increase in body weight that was a consequence of aging. There was no significant effect of age on heart rate or LV systolic pressure.

Variables of resting and stress LV function are displayed in Table 2. There were no significant differences among the age groups with respect to LV end-diastolic pressure. However, resting LV $dP/dt$, resting and peak cardiac index, and LV peak developed pressure were significantly decreased at 23 mo. Tau, a measure of LV relaxation, was increased in sham-23 rats compared with all younger age groups.

Indexes of LV remodeling and quantification of myocardial hypertrophy and fibrosis for the four groups are displayed in Table 3. In sham rats, LV end-diastolic volume index gradually increased with age, with a

| Table 1. Changes in body weight, heart chamber weight, left ventricular weights, heart rate, and left ventricular systolic pressure in sham-operated adult and infarcted aging rats |

<table>
<thead>
<tr>
<th>Body Weight, g</th>
<th>LV, mg</th>
<th>RV, mg</th>
<th>LV/Body Weight, mg/g</th>
<th>HR, beats/min</th>
<th>LV SP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-7</td>
<td>433 ± 75</td>
<td>848 ± 102</td>
<td>189 ± 48</td>
<td>1.93 ± 0.15*</td>
<td>358 ± 31</td>
</tr>
<tr>
<td>Sham-12</td>
<td>511 ± 40</td>
<td>804 ± 63</td>
<td>200 ± 28</td>
<td>1.60 ± 0.11</td>
<td>361 ± 49</td>
</tr>
<tr>
<td>Sham-18</td>
<td>565 ± 55†</td>
<td>894 ± 38</td>
<td>222 ± 22</td>
<td>1.58 ± 0.13</td>
<td>351 ± 22</td>
</tr>
<tr>
<td>Sham-23</td>
<td>610 ± 78†</td>
<td>1,021 ± 104</td>
<td>239 ± 45</td>
<td>1.70 ± 0.24</td>
<td>321 ± 32</td>
</tr>
<tr>
<td>M1-12</td>
<td>473 ± 56</td>
<td>806 ± 173</td>
<td>338 ± 145</td>
<td>1.68 ± 0.28</td>
<td>334 ± 45</td>
</tr>
<tr>
<td>M1-23</td>
<td>584 ± 43</td>
<td>1,013 ± 107</td>
<td>396 ± 122</td>
<td>1.72 ± 0.19</td>
<td>319 ± 21</td>
</tr>
<tr>
<td>Main effect</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.466</td>
<td>0.001</td>
</tr>
<tr>
<td>Disease</td>
<td>0.554</td>
<td>0.432</td>
<td>0.001</td>
<td>0.307</td>
<td>0.175</td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.546</td>
<td>0.001</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.470</td>
<td>0.275</td>
<td>0.784</td>
<td>0.474</td>
<td>0.275</td>
</tr>
</tbody>
</table>

Values are means ± SD. HR, heart rate; LV, left ventricle; LV/Body Weight, left ventricular weight/body weight; LV SP, left ventricular systolic pressure; RV, right ventricle; Sham-7, sham 7 mo; Sham-12, sham 12 mo; M1-12, infarcted 12 mo; Sham-18, sham 18 mo; Sham-23, sham 23 mo; M1-23, infarcted 23 mo. No. of rats (N) varies between 8 and 13 for all data. *$P < 0.05$ versus Sham-12, Sham-18, and Sham-23; †$P < 0.05$ versus Sham-7 and Sham-12; and ‡$P < 0.05$ versus Sham-7, Sham-12, and Sham-18. Interaction statistical analyses apply to Sham-12, M1-12, Sham-23, and M1-23.
Table 2. Variables of resting and stressed left ventricular performance in sham-operated adult and infarcted aging rats

<table>
<thead>
<tr>
<th></th>
<th>LV EDP, mmHg</th>
<th>dP/dt, mmHg/ls</th>
<th>Tau, ms</th>
<th>CI, ml·min⁻¹·kg⁻¹</th>
<th>CIw, ml·min⁻¹·kg⁻¹</th>
<th>PDP, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-7</td>
<td>3.7 ± 2.9</td>
<td>8,896 ± 901</td>
<td>14.1 ± 2.7</td>
<td>33.8 ± 4.1</td>
<td>67.6 ± 8.6</td>
<td>224 ± 15</td>
</tr>
<tr>
<td>Sham-12</td>
<td>5.9 ± 4.1</td>
<td>9,012 ± 988</td>
<td>11.3 ± 0.8</td>
<td>37.2 ± 6.4</td>
<td>68.0 ± 19.2</td>
<td>230 ± 13</td>
</tr>
<tr>
<td>Sham-18</td>
<td>5.8 ± 2.2</td>
<td>8,917 ± 971</td>
<td>13.4 ± 1.4</td>
<td>33.6 ± 4.8</td>
<td>66.8 ± 6.4</td>
<td>227 ± 15</td>
</tr>
<tr>
<td>Sham-23</td>
<td>6.2 ± 3.8</td>
<td>7,248 ± 957a</td>
<td>15.0 ± 2.1</td>
<td>28.5 ± 7.84</td>
<td>57.2 ± 10.84</td>
<td>211 ± 8†</td>
</tr>
<tr>
<td>MI-12</td>
<td>21.2 ± 9.6</td>
<td>5,827 ± 2,382</td>
<td>18.5 ± 6.8</td>
<td>32.6 ± 6.8</td>
<td>44.5 ± 10.5</td>
<td>191 ± 45</td>
</tr>
<tr>
<td>MI-23</td>
<td>17.3 ± 8.9</td>
<td>5,971 ± 1,498</td>
<td>16.8 ± 3.1</td>
<td>30.1 ± 5.9</td>
<td>44.1 ± 12.6</td>
<td>175 ± 44</td>
</tr>
</tbody>
</table>

Main effect 0.066 0.006 0.007 0.194 0.001 0.038
Disease 0.023 0.201 0.012 0.439 0.001 0.019
Age 0.585 0.005 0.067 0.125 0.257 0.431
Interaction 0.130 0.667 0.197 0.240 0.399 0.502

Values are means ± SD. CI, cardiac index; CIw, peak cardiac index; LV EDP, LV end-diastolic pressure; PDP, peak developed pressure; Tau, time constant of LV relaxation. N varies between 6 and 13 for all data. †P < 0.05 versus Sham-7, Sham-12, and Sham-18. Interaction statistical analyses apply to Sham-12, MI-12, Sham-23, and MI-23.

Effects of aging after MI. Data are presented as sham-12, MI-12, sham-23, and MI-23. Mortality for the first 24 h after coronary artery ligation was 56% for 7-mo-old rats and 60% for 18-mo-old rats. Table 1 shows body weights, heart chamber weights, LV-to-body weight ratio, heart rate, and LV systolic pressure for sham and infarct rats 4–5 mo after operation. Body weight and LV weight were significantly increased as a result of age, but not MI, whereas right ventricular weight increased only as a result of MI. Heart rate decreased with age but not with MI. There were no significant interactions of age and MI on any of these variables.

Data on resting and LV performance after maximal afterload and preload are shown in Table 2. LV end-diastolic pressure and tau increased as a result of disease, whereas age had no further influence on this variable. The first derivative of LV pressure with respect to time (dP/dt), peak cardiac index but not resting cardiac index, and LV peak developed pressure were decreased by MI. There were no significant interactions of age and MI on any variable of LV performance.

Table 3 shows the influence of aging and MI on variables of LV and myocardial remodeling. Compared with all sham groups, LV end-diastolic volume index was significantly increased after MI. However, there was no significant difference in LV end-diastolic volume index in young and old rats after MI. To determine whether differences in LV end-diastolic volume index among the groups were due to differences in the operating end-diastolic pressure (shifts along the same pressure-volume curve) or due to translations of the pressure-volume curves themselves, we calculated LV
Table 4. Papillary muscle mechanics in sham-operated young adult and aging rats

<table>
<thead>
<tr>
<th>group</th>
<th>DT, g/mm²</th>
<th>dT/dt, g·mm⁻²·s⁻¹</th>
<th>dT/dt, g·mm⁻²·s⁻¹</th>
<th>TPT, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-12</td>
<td>3.42 ± 0.41</td>
<td>35.5 ± 3.1</td>
<td>16.6 ± 2.4</td>
<td>159 ± 19</td>
</tr>
<tr>
<td>Sham-23</td>
<td>3.07 ± 0.39</td>
<td>25.1 ± 4.2 *</td>
<td>11.7 ± 3.5 *</td>
<td>192 ± 21*</td>
</tr>
</tbody>
</table>

Values are means ± SD. DT, peak developed tension; +dT/dt, maximum positive time derivative of developed tension; −dT/dt, maximum negative time derivative of developed tension; TPT, time to peak developed tension. N = 8 rats in each group. *P < 0.05 versus Sham-12.

Volume index at a common pressure of 10 mmHg. The results were as follows: sham-7 rats, 0.93 ± 0.03; sham-12 rats, 0.97 ± 0.18; sham-18 rats, 0.94 ± 0.17; sham-23 rats, 0.92 ± 0.21; MI-12 rats, 1.52 ± 0.16; and MI-23 rats, 1.44 ± 0.31 ml/kg. One-way ANOVA for all six groups indicated significant differences (P < 0.05) for MI compared with sham rats. There were no significant differences in LV diastolic volume index at 10 mmHg among sham rats or MI rats.

MI tended (P = 0.0882) to increase Kc, with no effect of age on this variable. Taken together, the results indicate that the pressure-volume curve was similar in shape and location in the pressure-volume plane for sham rats but translated to the right for MI rats. Percent fibrosis increased to a greater extent in MI-12 rats compared with MI-23 rats, resulting in a significant interaction of age and MI on this variable of myocardial remodeling. Myocyte hypertrophy, as measured by myocyte CSA, was significantly increased in the younger rats as a result of MI but did not increase further in old rats after MI. There were no differences in V/Vw among the four groups.

DISCUSSION

Despite the clinical importance of heart failure after MI in the aging population, there are, to our knowledge, no studies that have evaluated the influence of aging on the effects of MI on long-term function and remodeling in the heart. The goals of the present study were to obtain information on LV function and remodeling in the stable compensated phase of heart failure due to coronary ligation in the aging rat and to test the hypothesis that aging rats would have more advanced LV dysfunction and more extensive remodeling than younger adult rats after MI. We used the F344XBN hybrid, which is currently recommended by the NIA for investigations of the cardiovascular effects of aging. Our results indicate that, after MI, LV function and structure were altered to a similar degree in aging rats as in younger rats, despite limited myocyte hypertrophy and more advanced myocardial fibrosis at baseline in the older rat.

LV remodeling and function in the F344XBN rat during aging. Cardiac adaptations of the aging F344XBN rat, at the myocardial and ventricular level, correspond very closely to those previously reported for the Fischer 344 rat (3, 4, 9, 11, 18). LV weight increased during aging such that, by 23 mo of age, LV weight increased by 20%. The increase in LV weight at 23 mo corresponded to the appearance of myocyte hypertrophy and increased fibrosis. Interestingly, right ventricular weight did not increase during growth and aging in our study, although previous work has shown that both cardiac chamber weights increase in parallel during maturation and aging in the Fischer 344 rats.

Global LV performance was maintained in the F344XBN rat until 23 mo of age, when there was evidence of depressed baseline and maximal LV function. Previous work has demonstrated that these abnormalities at the ventricular level reflect alterations in the mechanical, biochemical, and electrical properties of the aging myocardium (1, 5, 9, 10, 14). In the present study, we also observed that papillary muscle mechanics, in particular with respect to time-dependent variables of contraction, are depressed in 23-mo-old rats, despite preservation of overall DT. However, although systolic function was decreased, there was no trend toward decompensation, given that LV end-diastolic pressures remained within the normal range. These data suggest that the design of studies in old rats needs to distinguish between the aging compensated and senescent decompensated heart.

Variables of LV remodeling were unchanged with aging in the F344XBN, except that the LV end-diastolic volume index was increased in sham-23 rats. However, LV volume index measured at the common pressure of 10 mmHg was similar for sham rats of all ages. Thus we concluded that the increased end-diastolic volume index in the sham-23 rats was primarily due to an increase in operating LV end-diastolic pressure. The interpretation that all sham groups operated along a similar pressure-volume curve was further supported by the similar values that were obtained for Kc and V/Vw. Although our analysis of LV volume and wall thickness is functional rather than morphometric, our data are consistent with those previously reported in the Fischer 344 rat. For example, V/Vw at a given pressure was similar at 7, 12, 18, and 23 mo of age in our study. This could happen only if chamber volumes and thicknesses were similar at the various ages or if chamber volumes and thicknesses increased in parallel to maintain the ratio. The latter is unlikely, since the shape of the pressure-volume curve, as indicated by Kc, was similar at all ages. In the Fischer 344 rat, LV chamber dimensions and wall thickness are maintained at 20 mo of age, although, at 29 mo, LV dilatation and mild wall thinning are evident (11).

Myocyte hypertrophy, as measured by cell CSA, and myocardial fibrosis were increased at 23 mo of age in the F344XBN. The mechanisms responsible for the appearance of myocardial hypertrophy and increased collagen content in the aged F344XBN are not clear. It has been postulated that spontaneous or programmed myocyte dropout leads to replacement fibrosis and a subsequent decline in contractile reserve, which engenders adverse ventricular remodeling, increased wall stress, and compensatory hypertrophy in remaining myocytes (11). Although an increase in LV afterload seems unlikely to account for myocyte hypertrophy, since neither LV peak systolic pressure in the present study nor mean arterial pressure (3) is increased in
aging rats, it is possible that LV wall stress was increased due to the increase in LV end-diastolic volume index.

LV remodeling and function after MI during aging. Our data indicate that, 5 mo after MI, LV remodeling and in vivo function decline to a similar degree in aging rats as in younger rats. These results were unexpected. Because experimental pressure (5, 10, 12, 16) and volume (15, 30) overload produce more extensive LV remodeling and mechanical dysfunction in aging rats than in mature adult rats, we had hypothesized that alterations in LV systolic function would be more severe, that LV remodeling would be more extensive, as reflected in the $K_e$ and $V/V_m$, and that myocardial hypertrophy would be less than in mature adult rats. One potential explanation for the differential response of the aging LV to MI versus that to pressure and volume overload is that each type of hemodynamic overload imposes unique conditions on wall stress; subsequently, those particular conditions that result from MI are better tolerated by the aging myocardium. For example, pressure overload produces marked elevations in LV systolic wall stress but not in diastolic wall stress (23), whereas volume overload produces increases in both systolic and diastolic wall stress (31). On the other hand, because LV end-diastolic pressure increases while LV peak systolic pressure declines after MI, LV diastolic wall stress may increase by up to ninefold from baseline, whereas systolic wall stress increases by a much smaller magnitude (24). Why an augmentation primarily in diastolic wall stress after MI should be better tolerated by the aging heart is not clear, but the reason may relate to myocyte growth mechanisms that are less age dependent when MI is the stimulus.

Another potential explanation for the equivalent degrees of LV alterations in remodeling and performance after MI in young and aging rats is that the most important determinant of LV performance and remodeling post-MI is the infarct size, so that the presence of a large MI and its subsequent effects on mechanical performance of the LV are more important than the amount of concentric or eccentric hypertrophy, baseline fibrosis, and level of LV function that was present before MI.

Last, it is possible that, although the rate of LV hypertrophy and the development of other compensatory changes are decreased in the aging myocardium, the extent to which the heart, with time, can compensate is not age dependent. For example, after acute hemodynamic overload, the rate and extent of myocardial hypertrophy is decreased in aging rats (15–17). However, after a longer duration of pressure overload, reactive myocardial hypertrophy in aged rats has been shown to be preserved (28). Furthermore, other investigators have shown that adequate long-term growth responses of the aging heart to various stimuli are sustained (6, 29). Finally, to explore whether alterations in the molecular control of myocyte growth could explain the diminished hypertrophic response of the aging myocardium to MI, a recent study compared mRNA expression of atrial natriuretic factor, a marker of myocyte cellular hypertrophy, and insulin-like growth factor in 4- and 16-mo-old Fischer 344 rats within 7 days of MI (13). The investigators found equivalent levels of atrial natriuretic factor, insulin-like growth factor, and the insulin-like growth factor receptor protein in both groups of rats, despite lesser relative myocyte hypertrophy in the older rats. Although it is possible that the insulin-like growth factor system engenders only a part of the adaptations of myocyte growth, it is also plausible that an equivalent degree of myocyte hypertrophy was not observed because the time points chosen for the study, 6 h to 7 days post-MI, were too early for a potentially delayed growth response in the aging myocytes to have occurred.

The finding that imposition of MI on the aging myocardium produces no further hypertrophy beyond that associated with aging alone suggests that age-associated myocyte hypertrophy is not caused by hemodynamic loading factors. Otherwise, one would have expected even more myocyte hypertrophy than we observed or worse LV performance due to the combined hemodynamic burdens of MI and aging. It is possible that myocyte hypertrophy associated with aging is induced by alterations in the gene program for cell growth that are independent of loading conditions and therefore can provide adequate myocardial reserve after imposition of MI.

Limitations. The purpose of this study was to compare the long-term effects of MI on LV performance and remodeling between young adult and aging rats. Although myocardial variables of hypertrophy and fibrosis were measured, the study was not designed to detect age-dependent functional responses to MI at the myocyte or myocardial level. It is possible that biochemical and molecular adaptations in the aging rat differ in degree and magnitude from those alterations that have been previously documented in younger rats after MI. Although these are important areas of future research, we believe our data will provide a framework within which the results of investigations into the biochemical and molecular responses of the aging heart to MI can be interpreted. Another limitation of the present study is that we did not assess LV performance and remodeling early after MI to test the hypothesis that the rate of adaptations in the aged heart was decreased. Finally, it is possible that, with a longer observation period than that of the current study, LV decompensation associated with an acceleration in the mortality rate would have been observed in the older cohort after MI. However, the current timeframe was chosen so that the period of compensated LV dysfunction after MI overlapped with age-related alterations in LV function and also to avoid the overt LV dysfunction (elevated LV end-diastolic pressure and dilated chamber) that has been described in the aged, senescent rats (11).

In conclusion, we found that, 5 mo after MI of equivalent size, mature adult and aging rats have a similar degree of LV dysfunction and remodeling. Furthermore, the extent of myocyte hypertrophy after MI was equivalent in both age groups. These data suggest that the aging, nonsenescent heart is not more vul-
nervable than the younger adult heart to moderate to large MI.

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