Induction of Myocardial Hypertrophy After Coronary Ligation in Rats Decreases Ventricular Dilatation and Improves Systolic Function

Sheldon E. Litwin, MD; Thomas E. Raya, MD; Peter G. Anderson, DVM, PhD;
Christine M. Litwin, MD; Rubin Bressler, MD; and Steven Goldman, MD

Background. Previous studies have shown that hypertrophy of surviving myocytes after myocardial infarction (MI) is limited. Progressive ventricular dilatation after MI may occur when compensatory hypertrophy cannot restore left ventricular (LV) wall stress to normal.

Methods and Results. To test whether induction of additional myocyte hypertrophy might prevent pathological LV remodeling after large MI, we administered 2-tetradecylglycidic acid (TDGA) 20 mg/kg/day to sham-operated (n=12) and MI (n=10) rats for 10 days, beginning the third day after infarction. We have previously shown that chronic inhibition of long-chain fatty acid oxidation with TDGA in rats results in myocardial hypertrophy without any apparent impairment of LV systolic function. When compared with untreated MI rats (n=9), we found that TDGA-treated MI rats had increases in LV weight/body wt, myocyte cross-sectional area, and peak developed LV pressure during abrupt aortic occlusion. MI rats treated with TDGA had lower LV end-diastolic pressures and smaller end-diastolic volumes, whereas stroke volume was maintained. The ex vivo passive LV pressure-volume relation was shifted toward the pressure axis compared with untreated infarct rats. In sham-operated rats, TDGA caused increases in LV weight/body wt, myocyte size, peak developed LV pressure, cardiac index, and stroke volume index, and a shift of the passive LV pressure-volume relation toward the pressure axis.

Conclusions. Induction of myocardial hypertrophy with an inhibitor of long-chain fatty acid oxidation retarded the process of LV dilatation and produced beneficial effects on systolic function after large myocardial infarction. These data support the hypothesis that inadequate hypertrophy of residual myocardium after infarction may contribute to LV dilatation and the development of congestive heart failure. (Circulation 1991;84:1819–1827)

Previous studies in humans and experimental animals have documented that progressive left ventricular (LV) dilatation may occur as a sequelae of myocardial infarction (MI).1–4 The presence of increased LV cavity volume after MI is a powerful predictor of subsequent mortality.5 The pathophysiology of postinfarction LV remodeling is not well understood, although it is clearly related to the presence of transmural necrosis and the size of the MI.6 It is commonly believed that chronic increases in diastolic wall stress predispose to LV dilatation.6,7

Although there is thinning of the noninfarcted LV wall, it has been previously demonstrated that there is enlargement of myocytes in the noninfarcted ventricular myocardium.7,8 Myocardial hypertrophy generally develops in response to increased load on the heart and is felt to be a beneficial compensatory mechanism that tends to normalize or lower elevated wall stress.9 According to Laplace’s law, LV wall stress is proportional to LV cavity radius and inversely proportional to LV wall thickness; hence, increases in these dimensions have opposite effects on wall stress. Based on the above relation, some
investigators have hypothesized that inadequate myocardial hypertrophy may allow increases in cavity volume to predominate in certain situations such as regurgitant valvular lesions or after MI. Although ventricular dilatation initially allows the heart to maintain stroke volume, this occurs at the expense of increased diastolic pressures and eventually culminates in the syndrome of congestive heart failure.

We have previously shown that chronic (7–28 days) administration of 2-tetradecylglyclic acid (TDGA), an inhibitor of long-chain fatty acid oxidation, results in myocardial hypertrophy in rats, with apparent preservation of LV systolic function and normal LV relaxation.10 Hearts from treated rats showed a pattern of concentric hypertrophy with decreased LV end-diastolic volume and a leftward shift of the passive LV pressure–volume relation. We undertook the current investigation in rats after large MI to determine 1) whether treatment with TDGA could augment the amount of hypertrophy that occurs in the noninfarcted myocardium, 2) if induction of this type of hypertrophy might prevent LV dilatation, and 3) if altering the process of LV remodeling was associated with beneficial hemodynamic effects. The hemodynamic and architectural alterations that develop in the left ventricle of the rat after large MI have been well characterized previously.3,4,11–14

Methods

Male Sprague-Dawley rats (Harlan Sprague Dawley, Indianapolis, Ind.) weighing 220–250 g were used for all studies. Rats underwent sham surgery or MI as described below and were randomized to no treatment or to TDGA treatment by using a lottery system. A nine-lead surface ECG was performed to screen for the presence of a large myocardial infarction 3 days after operation.13–15 Treatment was initiated immediately after ECG screening and subsequent randomization. TDGA (McNeil Pharmaceutical, Fort Washington, Pa.) was suspended in gum tragacanth solution and administered at a dose of 20 mg/kg/day by gastric gavage. This dose was chosen after performing a preliminary dose–response study with TDGA. Treatment was continued for 10 days. Hemodynamic studies were performed approximately 3 hours after the last dose of the drug. This duration of treatment was chosen because previous studies from our laboratory have shown that LV end-diastolic volume increases rapidly during the first 14 days after MI but increases at a much slower rate between 14 and 42 days after MI.4,13 The number of rats (8–12 in each group) was chosen to have a power of 0.8 to detect a 30% difference in LV end-diastolic volume between treated and untreated MI rats based on measurements made in previous studies.

Production of Myocardial Infarction

After induction of anesthesia with acepromazine maleate (TechAmerica, Kansas City, Mo.) 50 mg/kg, xylazine 5 mg/kg (Miles Laboratory, Shawnee, Kan.), and ketamine HCl (Parke Davis, Morris Plains, N.J.) 50 mg/kg i.p., a left anterior thoracotomy was performed under sterile conditions. The heart was expressed through the incision and a 7-0 synthetic ligature was secured snugly around the proximal left coronary artery. The lungs were inflated to reduce the pneumothorax, and the muscle layer and skin were closed separately. Postoperative analgesia was obtained with acetaminophen (67 mg/l) in the drinking water.

Evaluation of Left Ventricular Function

Rats were anesthetized with thiobutabital (Inactin, Buikulden Pharmaceutical, Konstan, FRG) 100 mg/kg i.p. A 3F micromanometer-tipped catheter (Millar Instruments Inc., Houston, Tex.) was inserted into the ascending aorta via the right carotid artery. The catheter was then advanced into the left ventricle under constant pressure monitoring. Zero baseline reference was obtained by placing the sensor in 37°C saline before insertion. LV dP/dt was obtained from a differentiating circuit in the physiological recorder (Gould 2400, Cleveland, Ohio). A fluid-filled polyethylene catheter (PE50) was inserted into the right external jugular vein by using a cutdown technique and was advanced to the right atrium. This catheter was connected to a 5F solid-state catheter (Millar Instruments) for monitoring of right atrial pressure.

After baseline hemodynamics were recorded, the trachea was intubated and the animals were ventilated with room air by a volume-cycled small animal ventilator (Model 683, Harvard Instruments, South Natick, Mass.). The chest was opened via a left anterior thoracotomy. The aorta was exposed and dissected away from the pulmonary artery. A snare was passed around the proximal aorta, and isovolumnic contractions were produced by abrupt occlusion of the aorta.10,11 Peak developed LV pressure was calculated as LV systolic minus LV end-diastolic pressure over the first five stable beats after aortic occlusion. This procedure was repeated two or three times, with 5–10 minutes allowed between occlusions for hemodynamics to return to baseline. A 3.5-mm internal diameter ultrasonic flow probe (T101, Transonic Systems Inc., Ithaca, N.Y.) was then placed around the ascending aorta. The LV catheter was pulled back to the ascending aorta and cardiac output (minus coronary flow) was recorded when it had been stable for at least 5 minutes. Just before the rats were killed, 0.1 ml of arterial blood was obtained for determination of the glucose level by using an Accuchek II glucose meter (Boehringer Mannheim Diagnostics, Indianapolis, Ind.).

Isolated Left Ventricular Pressure–Volume Relations

Pressure–volume data were recorded using previously described methods.3,4,10,13 At the conclusion of hemodynamic measurements, potassium chloride (2 mEq/ml) was injected through the right atrial catheter to arrest the heart. The heart was rapidly removed and the right ventricle was incised. A double-lumen catheter, attached to a pressure transducer (Statham 23 Id) and an infusion pump (Sage 341,
Cambridge, Mass.) was passed into the left ventricle. The atrioventricular groove was identified, and a ligature was passed around the heart and tied to isolate the left atrium from the left ventricle. After gentle aspiration of the volume ligature was residual blood, normal saline was infused at 0.70 ml/min into the suspended left ventricle while pressure was recorded. Saline was infused until the pressure increased to 40 mm Hg. Two or three curves were obtained from each ventricle within 10 minutes of cardiac arrest before the onset of rigor mortis.

From the pressure–volume data recorded ex vivo, the overall chamber stiffness constant $K_v$ was determined. At least 15 pairs of simultaneous pressure–volume points from each curve were digitized and stored. The pressure–volume data were fitted to the monoexponential equation

$$P = P_0 e^{K_v V} + P_B$$

(mean correlation coefficient $r = 0.97 \pm 0.03$) where $P$ and $V$ are pressure and volume, respectively, and $P_0$ and $P_B$ are modeling constants. Differentiating this equation with respect to volume yields

$$dP/dV = K_v (P - P_B)$$

$dP/dV$ is calculated numerically from the continuous pressure recording and plotted versus pressure. $K_v$ and $P_B$, the pressure intercept, are calculated by the method of least squares. This derivation allows for the possibility of the curve passing through the zero pressure–volume point. Operating chamber stiffness ($C_v$) was defined as

$$C_v = K_v (P_{ED} - P_B)$$

where $P_{ED}$ equals end-diastolic pressure measured in the closed-chest, anesthetized animal.

**Cavity/Wall Volume**

Ventricular cavity volume at a distending pressure of 10 mm Hg was determined from the passive pressure–volume relation. After completion of the pressure–volume recordings, the heart was separated into right ventricle and left ventricle plus septum and was then weighed. Left ventricular wall volume ($V_W$) was determined using the equation

$$V_W = \frac{LV \text{ mass}}{1.05}$$

where density of muscle equals 1.05. Operating end-diastolic volume was calculated from the pressure–volume curves by using the measured end-diastolic pressure from the anesthetized rat (Figure 2).

**Infarct Size**

After being weighed, the left ventricle was immersion-fixed in 10% buffered formalin. At a later time, the ventricle was cut into four transverse sections from apex to base. These sections were processed in standard fashion and embedded in paraffin. A trichrome-stained thin section from each level was projected, and the perimeters of the infarcted and noninfarcted epicardial and endocardial surfaces were traced and digitized. Infarct size is reported as the mean percent of the LV perimeter that was infarcted.

**Histological Studies**

For light and electron microscopy, rats in each treatment group were heparinized, and the hearts were quickly removed following the hemodynamic studies. The aorta was cannulated and perfused in a retrograde fashion at 100 mm Hg pressure with ice-cold saline solution followed by 2.5% glutaraldehyde in phosphate buffer for 15 minutes. Ten transmural tissue samples (approximately $3 \times 8 \times 1$ mm in size) from various locations in the left ventricle were postfixed in 1% osmium tetroxide, en bloc stained with uranyl acetate, and embedded in Spurr epoxy resin. Serial 1-μm sections from each block were affixed to a glass slide and stained with toluidine blue for light microscopic evaluation. From these sections, representative areas were identified, the tissue blocks were trimmed, and ultrathin sections were cut for examination on a Phillips 400 transmission electron microscope.

Morphometric analysis of the tissue was performed by previously described methods. Briefly, the trichrome stain of each section was projected at a magnification of $\times 1,100$ by using a binocular microscope attached to a video camera. This system was interfaced to a personal computer equipped with morphometric software (BIOQUANT TM SYSTEM IV, R and M Biometrics Co., Nashville, Tenn.). The circumferences of 15–20 myocytes cut in cross section were traced and digitized for each of the four sections from all hearts. Thus, a total of 60–80 myocytes were measured for each heart. Portions of the tissue where cell borders could be clearly identified and where the myocytes were the most round in shape were used for all measurements. The operator was blinded to the experimental group during the analysis.

**Statistical Analysis**

All results are presented as mean±SD. A two-way analysis of variance was used to test for the main effects (TDGA: yes/no; MI: yes/no) and interactions between TDGA treatment and MI. Differences between individual groups were detected using the Student-Newman-Keuls multiple comparisons test where appropriate. This allowed us to specifically compare the sham with the TDGA-sham rats and the MI with the TDGA-MI rats. Chamber stiffness constants and regression coefficients were determined by linear regression by the method of least squares. Significance was defined as a probability of less than 0.05.

**Results**

Body weights were not significantly different between any of the experimental groups (Table 1). Compared with shams, right ventricular (RV) weight and RV/body wt were increased in untreated MI rats. RV weight and RV/body wt were also increased in the TDGA-treated sham and MI rats compared with the
untreated sham and MI rats. LV weight was decreased in the untreated MI rats compared with the shams, although LV/body wt was not different. LV weight and LV/body wt were increased in the TDGA-treated sham and MI rats compared with the untreated sham and MI rats, respectively. Glucose values were not changed by treatment with TDGA in the sham rats but were increased by treatment in the MI rats. Infarct size ranged from 40% to 60% and was not different in the TDGA-treated and untreated MI rats (49±4% versus 52±8% of LV circumference). LV myocyte cross-sectional areas were significantly increased in MI rats compared with shams and were increased in both TDGA-treated groups compared with the untreated sham and MI rats (Figure 1).

Ventricular Geometry and Passive-Elastic Properties

Untreated MI rats had marked LV dilatation compared with sham-operated rats (Table 2). This is seen graphically as a rightward shift of the passive LV pressure–volume relation, so that any given pressure is associated with a higher volume (Figure 2). LV end-diastolic volume and V/Vw were significantly increased in the MI rats (Table 2). The overall LV chamber stiffness constant was decreased in rats with MI; however, operating chamber stiffness (C3) was increased in the untreated MI rats because they were operating on a steeper portion of their pressure–volume curve.

Compared with the untreated MI rats, TDGA-treated MI rats had a leftward shift of the LV pressure–volume relation and decreases in LV end-diastolic volume and V/Vw. Similarly, when compared with untreated sham rats, TDGA-treated sham rats also had a leftward shift of the passive LV pressure–volume relation and decreases in LV end-diastolic volume and V/Vw.

Hemodynamic Effects of TDGA Treatment

Hemodynamic parameters in anesthetized rats from each group are shown in Table 3. Compared with control rats, untreated MI rats had significant decreases in mean arterial pressure, LV systolic pressure, LV dP/dt, and peak developed LV pressure. Right atrial pressure and LV end-diastolic pressure were increased in MI rats. Cardiac index and stroke volume index were not different between control and MI rats.

TDGA produced an increase in peak developed LV pressure, lower right atrial pressure, and LV end-diastolic pressure in treated MI rats compared with untreated MI rats. Sham rats treated with TDGA had increased peak developed LV pressure, cardiac index, and stroke volume index compared with untreated shams.

Pathological Studies

Figure 3 shows representative cross sections of trichrome-stained left ventricle below the level of the

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Bar graph showing myocyte cross-sectional area for each of the four groups of rats. MI, myocardial infarction; TDGA, tetradecylglycidic acid administered at a dose of 20 mg/kg/day for 10 days after MI. Bars represent mean±SD of 60–80 myocytes per heart measured (sham, n=6; sham-TDGA, n=8; MI, n=7; and MI-TDGA, n=8).

---

**Table 1.** Body Weights, Heart Weights, and Glucose in Untreated and Tetradecylglycidic Acid–Treated Sham-Operated Rats and Rats With Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Body weight (g)</th>
<th>RV (mg)</th>
<th>LV (mg)</th>
<th>LV/Body wt (mg/g)</th>
<th>RV/Body wt (mg/g)</th>
<th>Glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n=12)</td>
<td>317±16</td>
<td>181±22</td>
<td>655±52</td>
<td>2.07±0.15</td>
<td>0.57±0.06</td>
<td>15±23</td>
</tr>
<tr>
<td>MI (n=9)</td>
<td>283±19</td>
<td>221±36*</td>
<td>580±49*</td>
<td>2.07±0.15</td>
<td>0.80±0.15*</td>
<td>156±54</td>
</tr>
<tr>
<td><strong>TDGA-treated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n=8)</td>
<td>306±7</td>
<td>217±24</td>
<td>768±41†</td>
<td>2.51±0.10†</td>
<td>0.71±0.07†</td>
<td>158±25</td>
</tr>
<tr>
<td>MI (n=10)</td>
<td>275±26</td>
<td>263±46</td>
<td>662±76</td>
<td>2.38±0.16*</td>
<td>0.95±0.20*</td>
<td>248±63‡</td>
</tr>
</tbody>
</table>

Statistics (p)

<table>
<thead>
<tr>
<th></th>
<th>Disease</th>
<th>Treatment</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0001</td>
<td>0.002</td>
<td>0.465</td>
</tr>
</tbody>
</table>

RV, right ventricular weight; LV, left ventricular weight; MI, myocardial infarction; TDGA, tetradecylglycidic acid administered at 20 mg/kg/day for 10 days after MI. All values are mean±SD. p values were obtained using two-way ANOVA. Intergroup comparisons were done by Student-Newman-Keuls test. *p<0.05 MI vs. sham; †p<0.05 sham-TDGA vs. sham; ‡p<0.05 MI-TDGA vs. MI.
papillary muscles from untreated and TDGA-treated MI rats. There is marked thinning of the noninfarcted wall as well as prominent cavity enlargement in the untreated rat. TDGA treatment produced obvious thickening of the noninfarcted segment and significantly decreased LV chamber dilatation. Higher power magnification of the area of noninfarcted myocardium directly adjacent to the infarct again demonstrates the significantly increased thickness of the noninfarcted myocardium of the TDGA-treated heart (Figure 4B) compared with the untreated heart (Figure 4A). There are no qualitative differences in the morphology of the myocardium of the treated and untreated hearts, and the character of the infarct is also similar in both groups. Figure 5 demonstrates the typical morphology of the infarct. This tissue contains a thickened epicardial surface, areas of granulation tissue with fibroblasts and macrophages, a central area of necrotic myocytes with no inflammatory reaction, and a thin rim of viable myocytes in the endomyocardium. This morphology is typical of a 14-day-old infarct, and there were no morphological differences in the infarcted tissue between the untreated and TDGA-treated hearts.

Electron microscopy of the noninfarcted regions of the untreated and treated hearts demonstrated normal ultrastructural morphology. Myocardial tissue from TDGA-treated hearts but not untreated hearts contained numerous round cytoplasmic droplets that are typical of lipid vacuoles (Figure 6). This finding is similar to our previous report of lipid droplets in the cytoplasm of TDGA-treated rats.10 Additionally, in both the untreated and TDGA-treated hearts, the myocardium adjacent to the infarct contained increased interstitial fibrous connective tissue. In Figure 6, fibroblast cell processes are visible between myocytes. This increased interstitial fibrous tissue was not present in areas distant from the area of infarction such as in the interventricular septum.

**Discussion**

It has previously been shown in experimental animals that hypertrophy of surviving myocytes occurs in proportion to infarct size for infarcts involving 0–20% of the left ventricle; however, there is little additional hypertrophy in infarctions larger than 20% of the left ventricle.8,16 In rats with infarction of less than 20% of the left ventricle, there are minimal or no changes in hemodynamics or peak pumping capacity of the heart.3,11 However, rats with larger infarctions develop increased LV filling pressures and a rightward shift of the passive LV pressure-volume relation.3,4,11–13 Therefore, it has been postulated that inadequate hypertrophy of residual myo-

---

**Table 2. Left Ventricular Geometry and Passive Chamber Stiffness in Untreated and Tetradecylglycidic Acid–Treated Sham-Operated Rats and Rats With Myocardial Infarction**

<table>
<thead>
<tr>
<th></th>
<th>LV EDVI (ml/kg)</th>
<th>V/Vw</th>
<th>Kc</th>
<th>Cs (mm Hg/ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n=11)</td>
<td>0.73±0.28</td>
<td>0.59±0.11</td>
<td>2.25±0.52</td>
<td>11.4±4.5</td>
</tr>
<tr>
<td>MI (n=7)</td>
<td>2.65±0.51*</td>
<td>1.01±0.18*</td>
<td>1.67±0.27</td>
<td>46.2±6.7*</td>
</tr>
<tr>
<td>TDGA-treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n=8)</td>
<td>0.53±0.26</td>
<td>0.50±0.05</td>
<td>2.28±0.32</td>
<td>14.3±4.3</td>
</tr>
<tr>
<td>MI (n=9)</td>
<td>1.63±0.58†</td>
<td>0.71±0.23†</td>
<td>1.67±0.22</td>
<td>35.9±10.2†</td>
</tr>
</tbody>
</table>

Statistics (p)

- Disease: 0.0001
- Treatment: 0.011
- Interaction: 0.090

LV EDVI, left ventricular end-diastolic volume calculated from the ex vivo pressure-volume relation and the measured LV end-diastolic pressure; V/Vw, LV cavity volume/LV wall volume at distending pressure of 10 mm Hg; Kc, LV chamber stiffness constant calculated from ex vivo passive LV pressure–volume relation; Cs, operating LV chamber stiffness calculated at measured LV end-diastolic pressure; MI, myocardial infarction; TDGA, tetradecylglycidic acid (20 mg/kg/day). All values are mean±SD. *p<0.05 MI vs. sham; †p<0.05 MI-TDGA vs. MI.

---

**Figure 2.** Graph showing passive left ventricular (LV) pressure–volume relations in untreated and tetradeacylglycidic acid (TDGA)-treated control rats and rats with myocardial infarction (MI). Curves are derived from the mean values of LV volume measured at different distending pressures in the rats from each group. Error bars represent standard deviation. LV end-diastolic pressure is indicated for each group and LV end-diastolic volume is estimated by extrapolating to the volume axis from this point (dotted lines).
### TABLE 3. Hemodynamic Parameters in Untreated and Tetradecylglycidic Acid–Treated Sham-Operated Rats and Rats With Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>RAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>PDP (mm Hg)</th>
<th>Cardiac index (ml/kg/min)</th>
<th>SVI (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n=12)</td>
<td>354±24</td>
<td>0.9±1.2</td>
<td>137±18</td>
<td>150±18</td>
<td>6±4</td>
<td>8,442±2,230</td>
<td>203±19</td>
<td>116±25</td>
<td>0.310±0.08</td>
</tr>
<tr>
<td>MI (n=9)</td>
<td>335±32</td>
<td>3.8±1.1*</td>
<td>96±8*</td>
<td>113±12*</td>
<td>28±2*</td>
<td>4,611±833*</td>
<td>129±11*</td>
<td>134±39</td>
<td>0.39±0.10</td>
</tr>
<tr>
<td><strong>TDGA-treated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham (n=8)</td>
<td>340±14</td>
<td>1.1±1.1</td>
<td>121±22</td>
<td>155±9</td>
<td>6±1</td>
<td>7,300±1,308</td>
<td>230±9</td>
<td>162±34†</td>
<td>0.43±0.07†</td>
</tr>
<tr>
<td>MI (n=10)</td>
<td>330±38</td>
<td>2.2±1.4‡</td>
<td>100±14</td>
<td>118±19</td>
<td>22±8‡</td>
<td>4,822±1,173</td>
<td>161±20‡</td>
<td>146±29</td>
<td>0.41±0.11</td>
</tr>
<tr>
<td><strong>Statistics (p)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>0.220</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.725</td>
<td>0.216</td>
</tr>
<tr>
<td>Treatment</td>
<td>0.220</td>
<td>0.230</td>
<td>0.322</td>
<td>0.385</td>
<td>0.079</td>
<td>0.794</td>
<td>0.0001</td>
<td>0.086</td>
<td>0.131</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.791</td>
<td>0.171</td>
<td>0.082</td>
<td>0.970</td>
<td>0.085</td>
<td>0.554</td>
<td>0.958</td>
<td>0.006</td>
<td>0.003</td>
</tr>
</tbody>
</table>

RAP, right atrial pressure; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, LV end-diastolic pressure; dP/dt, peak rate of LV pressure rise; PDP, peak developed LV pressure during transient aortic occlusion; SVI, stroke volume index; MI, myocardial infarction; TDGA, tetradecylglycidic acid (20 mg/kg/day). All values are mean±SD. *p<0.05 MI vs. sham; ‡p<0.05 sham-TDGA vs. sham; †p<0.05 MI-TDGA vs. MI.

Cardiomyocytes are sensitive to mechanical forces and pathological conditions, which can lead to progressive left ventricular (LV) dilatation after myocardial infarction (MI). Cardiac remodeling, often characterized by wall thickening and chamber enlargement, occurs as the body attempts to maintain adequate blood flow. The extent of remodeling is influenced by the degree of myocardial injury and the ability of the heart to adapt to the reduced contractile mass. In cases of severe infarction, the pressure-volume relationship may be altered, with an increase in end-diastolic pressure (LVEDP) and a decrease in cardiac output. The heart rate, which usually increases immediately after MI, may also reflect the body's attempt to maintain perfusion to vital organs. These adaptations are critical for short-term survival but may contribute to chronic heart failure if not managed effectively. The use of interventions such as pharmacological agents or mechanical support devices may be necessary to mitigate adverse remodeling and improve functional outcomes. 

**FIGURE 3.** Photomicrographs of left ventricular cross section below the level of the papillary muscles from untreated rat with myocardial infarction (MI) (panel A) and rat treated with tetradecylglycidic acid TDGA after MI (panel B). Both animals were killed 14 days after MI. Infarct size, expressed as percent of LV circumference replaced by scar tissue, was 52% in panel A and 49% in panel B. Note marked increase in thickness of noninfarcted LV lateral wall and septum in treated rat. Trichrome stain; bar, 1 mm.

Much attention has been focused on preventing LV dilatation after MI by early reperfusion of the infarct artery or by pharmacological reduction of preload and afterload in the postinfarct period. Both approaches appear to have been partially successful in this regard. In addition, the administration of medications that target specific pathways involved in cardiac remodeling has shown promise in limiting adverse LV remodeling. Further research is needed to identify predictors of adverse remodeling and to develop strategies that can effectively prevent or reverse this process.
of thyroid hormone to rats for 10–12 days after MI causes an increase in LV/body wt and a positive inotropic effect but no improvement in LV filling pressures. The persistently high LV end-diastolic pressures in thyroxine-treated MI rats may be attributable to the peripheral circulatory effects of thyroxine. To our knowledge, no previous studies have been done that specifically attempted to favorably influence LV remodeling after MI by inducing hypertrophy of the noninfarcted myocardium.

Increased LV wall stress is believed to be a potential cause of ventricular remodeling after MI. Although it is difficult to calculate wall stress in a segmentally infarcted ventricle, the law of Laplace suggests that increasing the thickness of the septum and noninfarcted free wall would lower LV wall stress if pressure remained constant. The recent observation that chronic inhibition of long-chain fatty acid oxidation in rats resulted in concentric LV hypertrophy with normal systolic performance afforded us the opportunity to further explore the pathophysiology of post-MI ventricular remodeling. TDGA was particularly well suited for our study because it appears to cause myocardial hypertrophy without altering LV loading conditions or myocardial function. Although the promotion of LV hypertrophy is unlikely to be beneficial in the setting of normal ventricular function, it could be a useful tactic in the setting of a compromised, dilated ventricle.

**Ventricular Geometry and Passive-Elastic Properties**

Our findings of increased myocyte cross-sectional area and LV/body wt in TDGA-treated MI rats indicate that it is possible to produce additional hypertrophy of noninfarcted myocardium. The histological studies and the finding of improved systolic reserve suggest that the increase in mass is due to increased myocyte volume rather than increases in fibrous tissue, extravascular fluid, or lipid infiltration. We were not able to measure hydroxyproline, water, or fat content of the ventricle because we felt it was necessary to do histological infarct sizing in all the rats. This is important because infarct size has been shown to be the major determinant of systolic dysfunction and LV dilatation in this model. Thus, a difference in infarct size between the groups would have biased the results. In a previous study, however, we showed that hypertrophied hearts from TDGA-treated rats did not have cellular or interstitial edema and that the amount of lipid accumulation did not account for the increase in LV mass.

In the present work, the increase in LV mass in the TDGA-treated MI rats was not associated with an increase in the LV chamber stiffness constant. LV
chamber stiffness is directly proportional to myocardial stiffness and inversely proportional to LV cavity volume and cavity/wall volume \((V/V_w)\). Because TDGA treatment produced decreases in both LV cavity volume and \(V/V_w\) but no change in chamber stiffness, it is tempting to speculate that TDGA treatment caused myocardial stiffness to decrease in the treated MI rats. However, it should be noted that the passive-elastic properties of the fibrous scar and the residual hypertrophied myocardium cannot be separated by the techniques used in these studies. Hypothetically, it is possible that improving pump function and decreasing LV dilatation with TDGA could lower LV wall stress and thus decrease the stimulus for fibrosis that typically occurs along with myocyte hypertrophy. This in turn could potentially decrease passive stiffness of the surviving myocardium.

The overall position of the passive LV pressure-volume curve was markedly shifted to the right in the untreated MI rats. TDGA treatment partially returned the curve toward the position of the sham group. The favorable effect on the position of the pressure-volume curve, in combination with a decrease in LV end-diastolic pressure, resulted in a significant decrease in LV end-diastolic volume in the TDGA-treated MI rats compared with the untreated MI rats. In addition, operating chamber stiffness, or the slope of the pressure-volume curve at operating end-diastolic pressure, was significantly decreased in the treated versus the untreated MI rats. This might be expected to improve LV filling dynamics.

**Left Ventricular Performance**

The degree of impairment in LV performance that we observed in untreated rats 14 days after MI is comparable to that reported between 5 and 42 days after MI in previous studies. Many indexes of LV performance are sensitive to changes in preload and/or afterload. Because mean arterial pressure was unchanged in TDGA-treated MI rats, it is unlikely that TDGA treatment altered afterload significantly. However, TDGA-treated MI rats had lower LV end-diastolic pressures and volumes, indicating a decrease in preload. Therefore, it is difficult to interpret the lack of improvement in baseline indexes of inotropic state (i.e., \(dP/dt\)) in the TDGA-treated MI rats compared with the untreated MI rats. Since peak developed LV pressure during aortic occlusion represents the maximal pressure-generating capability of the ventricle, this index can be used to compare function of different ventricles with less concern about differences in baseline loading conditions. The
finding of increased peak developed LV pressure during a maximal increase in afterload in the TDGA-treated MI rats indicates that systolic reserve was improved in this group. It is important that stroke volume was maintained in the TDGA-treated MI rats even though LV end-diastolic volume was decreased. This indicates that the TDGA-treated MI rats operated on a more favorable portion of their LV pressure–volume curve and had a higher ejection fraction.

**Clinical Implications**

There has been interest in the use of pharmacological agents that inhibit fatty acid oxidation for a variety of clinical purposes. TDGA was initially developed as an oral hypoglycemic agent because of its ability to promote glucose metabolism.\(^{23}\) It has also been proposed that agents in this general class may limit infarct size or prevent reperfusion injury by blocking the accumulation of toxic long-chain acylcarnitine compounds in the ischemic zone.\(^{24}\) Because of a paucity of data on the potential long-term effects of these agents in humans, it would be premature to predict that they may have a role in the treatment of postinfarction heart failure. Rather, we believe our findings are most useful in helping to clarify the cause of ventricular dilatation after MI. In rats, increasing the mass of the noninfarcted myocardium without altering the inotropic state resulted in improved LV geometry and function. It is possible that therapy with growth factors that could promote hypertrophy of the residual myocardium might have a future role in the prevention of pathological ventricular remodeling after MI.

**References**


**KEY WORDS** · myocardial infarction · ventricular remodeling · fatty acids · wall stress
Induction of myocardial hypertrophy after coronary ligation in rats decreases ventricular dilatation and improves systolic function.

S E Litwin, T E Raya, P G Anderson, C M Litwin, R Bressler and S Goldman

Circulation. 1991;84:1819-1827
doi: 10.1161/01.CIR.84.4.1819

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/84/4/1819