Postinfarction Survival and Inducibility of Ventricular Arrhythmias in the Spontaneously Hypertensive Rat Effects of Ramipril and Hydralazine

Tan Nguyen, BSc; Elias El Salibi, BSc; Jean L. Rouleau, MD

Background—Hypertensive patients with left ventricular hypertrophy (LVH) have been found to have greater peri–myocardial infarction (MI) and postinfarction mortality. In this study, we evaluated the postinfarction survival, susceptibility to ventricular arrhythmias, and degree of LVH and cardiac fibrosis in the spontaneously hypertensive rat (SHR) and the effects of the ACE inhibitor ramipril and the direct vasodilator hydralazine on these characteristics.

Methods and Results—An acute myocardial infarction (MI) was produced by ligation of the left anterior descending coronary artery. Rats were randomized to either control (n=50), hydralazine (n=41), or ramipril (n=45). Treatments were started 4 hours after infarction and continued for 8 weeks. Ramipril and hydralazine reduced arterial pressure similarly. Medications were stopped 72 hours before euthanasia, at which time hemodynamic, programmed electrophysiological stimulation (PES), and morphological studies were performed. Mortality was decreased in ramipril (56%) compared with hydralazine (78%) and control (82%) SHRs (P=0.008). This was accompanied by a decrease in myocardial hypertrophy and fibrosis and a decrease in inducibility of ventricular arrhythmias by PES in the ramipril group regardless of MI size. Treatment with hydralazine had little or no effect on LVH and cardiac fibrosis and did not modify inducibility of ventricular arrhythmias by PES. Ramipril but not hydralazine prevented the increase in LV end-diastolic pressure in rats with large MIs.

Conclusions—In the SHR, the ACE inhibitor ramipril reduces LVH, cardiac fibrosis, and susceptibility to ventricular arrhythmias by PES and improves survival and LV function. Despite a similar decrease in arterial pressure, hydralazine does not have these beneficial effects. (Circulation. 1998;98:2074-2080.)

Key Words: hypertrophy ▪ myocardial infarction ▪ ramipril ▪ arrhythmias ▪ fibrosis

Patients with hypertension have been found to have a greater peri–myocardial infarction (MI) and postinfarction mortality rates than normotensive patients. Why this occurs is uncertain and is probably related to a number of different factors. The increased mortality rate may be related to increased risk of myocardial ischemia due to vascular changes and increased afterload and/or to an increase in susceptibility to ventricular arrhythmias resulting from the increased myocardial fibrosis and hypertrophy associated with hypertension. Also, ventricular remodeling after infarction and its effects on ventricular function may be different in patients with hypertension and left ventricular hypertrophy (LVH).

ACE inhibitors have been found to be the most effective drugs in attenuating ventricular remodeling, preserving ventricular function, and improving survival after large myocardial infarction. At this time, few data on postinfarction ventricular remodeling and the effects of therapy in hypertensive patients exist. Two studies done in the spontaneously hypertensive rat (SHR) suggest that postinfarction ventricular dilatation in the SHR is at least as marked if not more so than in normal rats and that the decrease in ventricular function that normally occurs in this setting may be greater. A study by Nishikimi et al suggests that ACE inhibitors may attenuate the loss of ventricular function and the changes in ventricular remodeling normally found after infarction in the SHR. Nevertheless, many important questions regarding survival, the characteristics of LV remodeling (such as the degree of cardiac fibrosis), changes in susceptibility to ventricular arrhythmias, and the effects of therapeutic interventions on these changes remain to be explored or resolved.

This study was thus undertaken in the SHR to answer the following questions: (1) What are some of the characteristics of LV remodeling after infarction, such as cardiac fibrosis and hypertrophy, in the setting of hypertension and LVH; (2) does the control of blood pressure after infarction in the SHR significantly modify remodeling and prognosis after infarction; (3) are these changes associated with an increased or decreased susceptibility to ventricular arrhythmias as assessed by programmed electrophysiological stimulation.
(PES); and (4) what are the effects of hydralazine and the ACE inhibitor ramipril on these variables in the SHR?

Methods

Preparation of Animals
A total of 136 male SHRs (body weight, 250 to 300 g; 13 weeks old) were obtained from Charles River Breeding Laboratories (Saint-Constant, Quebec, Canada). Their care and all procedures were in accordance with the Canadian Council for Animal Care and the Animal Care Committee of the Montreal Heart Institute.

Systolic Blood Pressure and Heart Rate Monitoring
Indirect systolic blood pressure and heart rate were determined by the tail-cuff method (Harvard Apparatus). The reported values are the mean of at least 3 recordings taken at the same time of day at baseline, before the infarction, and at 4 and 7 weeks after infarction.

Myocardial Infarction
Myocardial infarction was induced in all SHRs after the baseline measurement of systolic blood pressure and heart rate (week 0) according to methods previously described.

Drug Randomization
Rats were randomly divided into 3 groups according to their therapeutic intervention 4 hours after infarction. One group received an intraperitoneal injection of normal saline solution and normal drinking water thereafter (control group, n = 50). A second group received an intraperitoneal injection of ramipril ( Hoechst-Marion-Roussel) (37.5 μg/kg body wt) followed by 7.5 mg/L in the drinking water (ramipril group, n = 45). A third group received an intraperitoneal injection of hydralazine (Sigma Chemical Co) (0.4 mg/kg body wt) followed by 80 mg/L in the drinking water (hydralazine group, n = 41). Only rats that survived for at least 72 hours after infarction were classified according to infarct size (at the end of the study).

Hemodynamic Measurements
After 8 weeks of antihypertensive therapy, all drugs were stopped 72 hours before the hemodynamic measurements to permit adequate washout. The rats were anesthetized with an injection of a ketamine-HCl (87 mg/kg IM) and rompun-xylazine (13 mg/kg IM) mixture. The heart was then stopped in diastole with a saturated potassium chloride solution, removed, and rinsed in saline solution. For rats that died during the PES preparation or during the 8 weeks of antihypertensive therapy, the heart was simply removed and rinsed in saline solution. The LV was then filled with saline solution to a pressure of 15 mm Hg, sealed, and fixed in its distended form in formalin. Two cross sections were obtained at 1-mm intervals midway between the base and the apex of the LV. Myocardial infarction size was determined from the 2 cross sections of the LV as previously described. A large MI was defined as involving ≥35% of LV circumference, and a small-to-moderate infarction as involving <35%. Collagen was quantified by computer-assisted image analysis of samples from both cross sections cut into 8-μm-thick slices and stained with Sirius red F3BA as a 0.1% solution in saturated aqueous picric acid. The details of the methodology have been described previously. The heavily fibrotic scar was excluded. An approximation of total collagen volume was obtained by multiplying the LV weight/body weight (LVW/BW) ratio by collagen volume density percent.

Programmed Electrophysiological Stimulation
At the end of the hemodynamic measurements, the thorax was opened by sternotomy and PES was done through Biomed electrodes (Cooner Wire Co) sewn onto the epicardial surface of the RV outflow tract, and recordings were made at the LV apex. Pacing was performed by means of a Bloom programmable stimulator (World Precision Instruments). The protocol for PES used in this study was similar to that described by Bélichard et al. The effective refractory period was determined by premature stimulation with a single extrastimulus after 20 paced beats at a basic cycle length of 100 ms. Induction of ventricular arrhythmias was then attempted by ventricular stimulation at a basic cycle length of 100 ms (S), with single (S), double (S), and triple (S) extrastimuli delivered after 20 paced beats (Figure 1).

The end point of PES was induction of a ventricular tachyarrhythmia consisting of at least 6 consecutive nondriven ventricular extrastimulus beats. A preparation was considered noninducible when PES produced either no ventricular premature beats or only self-terminating salvos of <6 beats. Distinction was not made between ventricular tachycardia and ventricular fibrillation. A ventricular tachyarrhythmia was considered nonsustained when it lasted ≤15 beats and sustained when it lasted >15 beats before terminating spontaneously or by overdrive pacing.

An arrhythmia scoring system was used: 0, noninducible preparations; 1, nonsustained tachyarrhythmias induced with 3 extrastimuli; 2, sustained tachyarrhythmias induced with 3 extrastimuli; 3, nonsustained tachyarrhythmias induced with 2 extrastimuli; 4, sustained tachyarrhythmias induced with 2 extrastimuli; 5, nonsustained tachyarrhythmias induced with 1 extrastimulus; 6, sustained tachyarrhythmias induced with 1 extrastimulus; and 7, tachyarrhythmias induced during the 20 paced beats at a basic cycle length of 100 ms. If the heart stopped before the PES, the arrhythmia score assigned to that heart was 8.

Morphological Studies
The heart was then stopped in diastole with a saturated potassium chloride solution, removed, and rinsed in saline solution. For rats that died during the PES preparation or during the 8 weeks of antihypertensive therapy, the heart was simply removed and rinsed in saline solution. The LV was then filled with saline solution to a pressure of 15 mm Hg, sealed, and fixed in its distended form in formalin. Two cross sections were obtained at 1-mm intervals midway between the base and the apex of the LV. Myocardial infarction size was determined from the 2 cross sections of the LV as previously described. A large MI was defined as involving ≥35% of LV circumference, and a small-to-moderate infarction as involving <35%. Collagen was quantified by computer-assisted image analysis of samples from both cross sections cut into 8-μm-thick slices and stained with Sirius red F3BA as a 0.1% solution in saturated aqueous picric acid. The details of the methodology have been described previously. The heavily fibrotic scar was excluded. An approximation of total collagen volume was obtained by multiplying the LV weight/body weight (LVW/BW) ratio by collagen volume density percent.

Statistics
All values are expressed as mean ± SD. A χ² test was used to evaluate the effects of different drugs on inducibility of ventricular arrhythmias and final mortality figures. One-way ANOVA was used to assess the effects of multiple comparisons, followed by a 2-sided...
TABLE 1. Effect of MI and Pharmacological Interventions on Heart Rate and Arterial Blood Pressure

<table>
<thead>
<tr>
<th>Baseline (Week 0)</th>
<th>Week 4 After Infarction</th>
<th>Week 7 After Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Rate, bpm</strong></td>
<td><strong>Arterial Pressure, mm Hg</strong></td>
<td><strong>Heart Rate, bpm</strong></td>
</tr>
<tr>
<td>Control</td>
<td>472±37 (n=50)</td>
<td>190±13 (n=50)</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>472±39 (n=41)</td>
<td>191±24 (n=41)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>476±34 (n=45)</td>
<td>189±16 (n=45)</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*P<0.05 vs control.
†P<0.05 vs baseline.

Figure 2. Postinfarction survival of the 3 groups.

Dunnett’s comparison test when appropriate. For the Kaplan-Meier survival curves, a log-rank comparison test was used.

Results

Survival

There was a high early (72 hours) postinfarction mortality, with 30 rats (60%) in the control group and 27 rats (65.9%) in the hydralazine-treated group dying (P=0.05 versus control) (Figure 2). Early postinfarction mortality was still relatively high in the ramipril-treated group, but it was less than in the other 2 groups (P=0.016 versus control; P=0.006 versus hydralazine), with 16 rats (35.6%) dying within 72 hours of the operative procedure. During the next 53 days, mortality in control rats with large infarctions (>35% of circumference) continued to be very elevated, with 9 of 11 rats dying (82%). Hydralazine-treated rats with large infarctions also had a high mortality, with 5 of 9 rats dying (56%) (P=0.566 versus control). Ramipril-treated rats with large infarctions fared somewhat better, with 7 of 16 rats dying (43%). Rats with smaller infarctions (≤35% of circumference) did well regardless of treatment, with 2 deaths out of 9 control rats (22%), 0 of 5 hydralazine-treated (0%) and 2 of 11 ramipril-treated (18%) rats with small-to-moderate MIs dying. Overall survival in control rats (9 of 50 [18%]) was very poor, as was overall survival in hydralazine-treated rats (9 of 41 [22%], P=0.878 versus control). The overall survival was thus best in ramipril-treated rats, with 20 of 45 (44%) surviving the entire 56 days (P=0.001 versus control; P=0.007 versus hydralazine).

Heart Rate and Blood Pressure

In the control group, systolic pressure fell significantly after the MI, but heart rate did not change (Table 1). A greater decrease in systolic arterial pressure occurred after infarction in both hydralazine- and ramipril-treated rats compared with controls (P<0.05). This decrease in systolic arterial pressure was accompanied by a significant increase in heart rate in hydralazine-treated (P<0.05 versus control) but not ramipril-treated rats.

Hemodynamic Measurements

Rats with small-to-moderate MIs (≥35% of circumference) had similar cardiac hemodynamics and end-diastolic pressures (LVEDP), regardless of treatment group (72 hours after stopping all drugs), except for heart rate, which continued to be greater in the hydralazine-treated rats (P<0.05 versus control) (Table 2). In control rats with large MIs, LV systolic pressure as well as LV positive and negative maximum rate of pressure change (dP/dt) were well preserved despite a large MI size (53%). However, LVEDP was increased. RV measurements were unchanged. Hydralazine-treated rats with large MIs had many of the same changes as control rats with large MIs despite a smaller MI size. The only exception was an increase in LVEDP, which only approached significance. Ramipril-treated rats with large MIs had significantly lower heart rates and LVEDP compared with the other 2 large-MI groups (P<0.05). Other differences were not significant compared with the other 2 large-MI groups.

Programmed Electrophysiological Stimulation

All but 1 control rat did not have ventricular arrhythmias induced by PES (Table 3, Figure 3). Another died during the preparation for the PES. Results were similar in hydralazine-treated rats, among which only 1 of 9 rats (11.1%) was not inducible by PES. Ramipril-treated hearts fared somewhat better, with 13 of 18 hearts (72.2%) not being inducible (P<0.05 compared with control and hydralazine). When the severity of the arrhythmia induced was considered by calculating the inducibility quotient (Figure 3), similar results were obtained, with ramipril-treated rats having a lower quotient than the other 2 groups regardless of whether one considers rats that died during the surgical preparation.

Morphological Characteristics

Ramipril-treated hearts had the greatest decrease in LVW/BW ratio compared with controls, regardless of MI size. Hydralazine-treated rats with small-to-moderate MIs had a significant but less marked decrease in LVW/BW ratio,
Discussion

Hypertension is a major risk factor for peri-infarction and postinfarction survival.1 ACE inhibitors improve survival in such patients.12 In this study, we demonstrate that postinfarction mortality in the SHR is extremely elevated and that this may be related to increased susceptibility to ventricular arrhythmias and to an increase in cardiac fibrosis and hypertrophy above the increase in these variables already known to exist in the SHR. Our results suggest that the poor postinfarction survival, further development of morphological abnormalities, and increased susceptibility of ventricular arrhythmia in the SHR appear to be largely independent of arterial pressure, because hydralazine had little effect on these characteristics despite normalizing arterial pressure. However, this study indicates that the ACE inhibitor ramipril improves postinfarction survival in the SHR and provides several mechanisms, independent of its hypotensive effect, by which it may do this. These include improved LV hemodynamic parameters, decreased cardiac fibrosis and hypertrophy, and decreased inducibility of ventricular arrhythmias by PES.

TABLE 3. Ventricular Arrhythmias Induced With PES

<table>
<thead>
<tr>
<th></th>
<th>Control (n=9, n%)</th>
<th>Ramipril (n=20, n (%))</th>
<th>Hydralazine (n=9, n)</th>
<th>Global χ²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninducible</td>
<td>1/8 (12.5)†</td>
<td>13/18 (72.2)</td>
<td>1/9</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT or VF</td>
<td>2/8 (25)</td>
<td>1/18 (5.6)</td>
<td>1/9</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Sustained VT or VF</td>
<td>5/8 (62.5)†</td>
<td>4/18 (22.2)</td>
<td>7/9</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Death during surgical preparation</td>
<td>1/9 (11.1)</td>
<td>2/20 (10.0)</td>
<td>0/9</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Noninducible (including death during surgical preparation)</td>
<td>1/9 (11.1)‡</td>
<td>11/20 (55.0)</td>
<td>1/9</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

VF indicates ventricular fibrillation; VT, ventricular tachycardia.
*P<0.05 vs control.
†P<0.05 vs ramipril.
‡P<0.1 vs ramipril.
§P<0.1 vs control.
azine are less certain because of the small number that survived 72 hours after infarction; however, the data that we do have suggest that it is no better than ramipril and may even be a bit worse.

The poor survival of these rats, coupled with the marked inducibility of ventricular arrhythmias by PES in the rats that survived, is consistent with an arrhythmic substrate being present in these hearts and contributing to their high mortality rate. Previous studies in the SHR,4,5,6 in other animal models of LVH,4,7 and in patients with LVH4 have all documented a relationship between LVH and susceptibility to ventricular arrhythmias. This susceptibility has been attributed to both increased cardiac fibrosis4,8 and cardiac hypertrophy.5 In this study, cardiac fibrosis and hypertrophy were greater in control and hydralazine-treated hearts than in ramipril-treated hearts and thus may have contributed to the high inducibility rate of ventricular arrhythmias by PES and mortality in these rats.

**Effects of Ramipril**

Treatment with the ACE inhibitor ramipril was associated with improved early and late survival. The beneficial effects of ramipril were most marked on early postinfarction survival, but late mortality in rats with large MIs receiving ramipril was also better.

Postinfarction mortality that occurs between 4 and 9 hours after infarction in this SHR model is due to ventricular arrhythmias with or without hemodynamic compromise.16 The origin of ventricular arrhythmias early after infarction appears to be the interface between dead and still viable myocardium, where depolarized myocytes can develop abnormal automaticity.17 How ramipril modifies this early arrhythmic phase, if indeed it does at all, is unknown but may involve a reduction in local as well as systemic neurohumoral activation. Also, although the infarction process is thought to be complete in normal rats by

**Control and Hydralazine-Treated SHRs**

Postinfarction survival in the control MI group was very poor. Most of these deaths occurred early, with 60% of all rats dying in the first 72 hours after infarction. Late mortality was particularly elevated in the control large-MI group, with only 2 of 11 (18%) 72-hour-postinfarction survivors with large MIs surviving the full 8 weeks. Such poor early and late postinfarction survivals in the SHR are compatible with studies in humans in which hypertensive patients were found to have a poor early and late postinfarction survival.1

Results from this study would suggest that when LVH is present, simple control of arterial pressure, such as that obtained with hydralazine, is insufficient to reduce early mortality. However, because hydralazine also increased heart rate, presumably due to reflex activation of the adrenergic system, in this study it cannot be determined whether another hypotensive agent that did not activate the adrenergic system, would have fared better. The effects on late mortality of controlling arterial pressure with hydralazine are less certain because of the small number that survived 72 hours after infarction; however, the data that we do have suggest that it is no better than ramipril and may even be a bit worse.

**TABLE 4. Cardiac Morphological Characteristics of Survivors 56 Days After Infarction**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=7)</th>
<th>Ramipril (n=11)</th>
<th>Hydralazine (n=5)</th>
<th>Control (n=2)</th>
<th>Ramipril (n=9)</th>
<th>Hydralazine (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survivor (56 days post-MI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BW, g</td>
<td>412±27</td>
<td>376±0.2*</td>
<td>347±0.2*</td>
<td>334±93*</td>
<td>362±25*</td>
<td>388±36†</td>
</tr>
<tr>
<td>LVW/BW, mg/g</td>
<td>3.45±0.3</td>
<td>2.68±0.3*</td>
<td>2.81±0.3*</td>
<td>3.04±0.9*</td>
<td>2.67±0.4*</td>
<td>3.00±0.3*</td>
</tr>
<tr>
<td>RWW/BW, mg/g</td>
<td>0.74±0.1</td>
<td>0.67±0.1</td>
<td>0.80±0.1</td>
<td>1.04±0.6*</td>
<td>0.93±0.2†</td>
<td>1.04±0.2*</td>
</tr>
<tr>
<td>MI, % circumference</td>
<td>15.3±11.1</td>
<td>17.3±11.5</td>
<td>28.9±7.4*</td>
<td>52.3±20.2*</td>
<td>52.4±11.5*</td>
<td>48.1±10.9*</td>
</tr>
<tr>
<td><strong>Days post-MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days post-MI</td>
<td>30.0±5.7</td>
<td>33.0±4.2§</td>
<td>…</td>
<td>27.3±10.7</td>
<td>33.6±6.6§</td>
<td>27.4±8.2</td>
</tr>
<tr>
<td>BW, g</td>
<td>331±4†</td>
<td>346±32†</td>
<td>…</td>
<td>282±46</td>
<td>315±25§</td>
<td>269±59</td>
</tr>
<tr>
<td>LVW/BW, mg/g</td>
<td>2.80±0.2†</td>
<td>2.15±0.1†</td>
<td>…</td>
<td>2.61±0.3</td>
<td>2.38±0.2†</td>
<td>2.59±0.6</td>
</tr>
<tr>
<td>RWW/BW, mg/g</td>
<td>1.00±0.2†</td>
<td>0.80±0.1†</td>
<td>…</td>
<td>1.22±0.1</td>
<td>0.88±0.1†</td>
<td>1.09±0.2†</td>
</tr>
<tr>
<td>MI, % circumference</td>
<td>15.4±17.8‡</td>
<td>33.2±0.8‡</td>
<td>…</td>
<td>50.2±9.3</td>
<td>53.6±3.6</td>
<td>57.5±8.9§</td>
</tr>
</tbody>
</table>

*For survivors, P<0.05 vs control small-to-moderate MI.
†For survivors, P<0.10 vs control small-to-moderate MI.
‡For death during treatment, P<0.05 vs control large MI.
§For death during treatment, P<0.10 vs control large MI.
Cardiac Fibrosis by Computer-Assisted Analysis

<table>
<thead>
<tr>
<th></th>
<th>Small-to-Moderate MI (≤35%)</th>
<th>Large MI (&gt;35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Ramipril</td>
</tr>
<tr>
<td>Survivor (56 days post-MI)</td>
<td>n=7</td>
<td>n=11</td>
</tr>
<tr>
<td>Collagen volume density, %</td>
<td>3.55±0.5</td>
<td>1.95±0.6*</td>
</tr>
<tr>
<td>Cardiac fibrosis</td>
<td>12.2±1.2</td>
<td>5.34±2.0*</td>
</tr>
<tr>
<td>Death during treatment (&gt;72 hours; &lt;56 days post-MI)</td>
<td>n=2</td>
<td>n=2</td>
</tr>
<tr>
<td>Days post-MI</td>
<td>30±6</td>
<td>33±4</td>
</tr>
<tr>
<td>Collagen volume density, %</td>
<td>2.53±0.5</td>
<td>2.34±0.5</td>
</tr>
<tr>
<td>Cardiac fibrosis</td>
<td>7.14±1.9</td>
<td>5.05±1.5§</td>
</tr>
</tbody>
</table>

Cardiac fibrosis = % collagen volume density × LW/BW. Values are mean±SD.

*P<0.05 vs survivors/control small-to-moderate MI group.
†P<0.05 vs survivors/control large MI group.
‡P<0.05 vs death during treatment/control large MI group.
§P<0.10 vs death during treatment/control small-to-moderate MI group.

4 hours after infarction, recent results by Anversa et al. suggest that progressive cell loss can occur for up to 7 days after infarction, such that another potential mechanism is reduction of cell loss in the peri-infarction region due to reduced myocardial energy requirements and improved coronary blood flow due to ramipril. 

The use of ramipril appeared to be associated with the preservation of ventricular function in hearts with large MIs. However, the difference in ventricular function between control rats and ramipril-treated rats with large MIs was less marked than that described in normal rats and by Nishikimi et al. in the SHR. This may have been the result of the small number of control SHRs with large MIs that survived until the hemodynamic portion of the study. Presumably, the rats that died before the end of the study had hemodynamic abnormalities that were at least as important as those that survived, such that our findings may underestimate the true level of abnormalities present in control SHRs with large MIs compared with their ramipril counterparts.

Acknowledgments

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References


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