Effects of pre-, peri-, and postmyocardial infarction treatment with omapatrilat in rats: survival, arrhythmias, ventricular function, and remodeling


DURING THE ACUTE PHASE of myocardial infarction (MI), the major cause of death is ventricular arrhythmias. Indeed, nearly 70% of patients dying of an acute MI die suddenly before reaching the hospital (11). The major goal of therapy once the patient reaches the hospital is reestablishing cardiac perfusion to limit MI size. Once MI is well established and the damage irreversible, one of the major objectives is to limit adverse left ventricular (LV) remodeling to reduce the risk of heart failure and other post-MI complications.

Drugs such as angiotensin-converting enzyme (ACE) inhibitors have been shown to be useful in improving outcome when started early after MI (1, 13, 18). A new class of drugs, the vasopeptidase inhibitors (VPIs), simultaneously inhibit the activity of both the ACE and neutral endopeptidase (NEP) enzymes. In a previous study (12), we showed that, when started 4 h after MI, omapatrilat improved LV remodeling, LV function, and survival. In another study (3), we demonstrated that the VPI omapatrilat reduced peri-MI mortality (4 days) in rats and that this beneficial effect could be blocked by the simultaneous administration of B1 and B2 bradykinin (BK) receptor antagonists. However, the number of rats in the peri-MI study was relatively small, and the mechanism by which BK was beneficial and whether these early benefits were sustained or lost over time were not assessed.

This study was thus undertaken 1) to confirm whether pre-, peri-, and post-MI omapatrilat improves peri-MI and early post-MI survival, and whether these early benefits are preserved over time, and 2) to determine the mechanisms by which this occurs. The mechanisms that we evaluated in assessing why omapatrilat improves survival were based on knowledge of the fundamental mechanisms involved in early and late post-MI survival, that is, ventricular arrhythmias, MI

vasopeptidase inhibitor

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size, LV remodeling, and function. Our hypotheses were 1) that omapatrilat would improve early post-MI survival, and that this benefit would be sustained, and 2) that omapatrilat would reduce ventricular arrhythmias, reduce MI size, and improve LV remodeling and function.

MATERIALS AND METHODS

Animals and Drug Regimen

The drug regimen is shown in Fig. 1. Sprague-Dawley rats (Charles River, St-Constant, QC, Canada), 9–10 wk old, received normal crushed laboratory chow with or without the VPI omapatrilat (20 mg·kg⁻¹·day⁻¹; Refs. 4, 5) starting 7 days before MI surgery. Omapatrilat inhibits both ACE (IC₅₀ = 5 nM) and NEP (IC₅₀ = 9 nM) and was provided for research purposes by Bristol-Myers Squibb (Princeton, NJ). To ensure adequate peri-MI levels of omapatrilat, an intraperitoneal injection of 2 mg/kg omapatrilat or saline (untreated control group) was administered 4 h after MI and again the next morning in survivors. Normal crushed laboratory chow with or without omapatrilat (20 mg·kg⁻¹·day⁻¹) was resumed after MI and continued for 24 h or 38 days according to the protocol (Fig. 1). All of the animal experiments followed the guidelines of the Canadian Council on Animal Care and were approved by the Animal Care Ethics Committee of the University Health Network (Toronto, ON, Canada).

Experimental MI

Rats were anesthetized with an intramuscular injection of a mixture of 50 mg/kg ketamine and 10 mg/kg xylazine, and a MI was induced by ligating the left anterior descending coronary artery as described by Nguyen et al. (17). Once awakened after surgery, the rats were injected intramuscularly with 0.01 mg/kg buprenorphine HCl (Reckitt Colman Pharmaceuticals, Richmond, VA) to reduce pain during recovery. The sham ligation group underwent a similar procedure except that the suture was not tightened around the coronary artery.

24-h Peri-MI Arrhythmia, Blood Pressure, and Survival Protocol

Ambulatory ECG and blood pressure monitoring. To assess the effects of the MI with and without omapatrilat on systemic arterial pressure and arrhythmias, 34 rats had surgery performed 8 days before MI, before medications were started, to install continuous ECG and blood pressure monitoring (Data Sciences International, St. Paul, MN). Rats were anesthetized with an intramuscular injection of a mixture of 50 mg/kg ketamine (Rogar/STB, Montreal, QC, Canada) and 10 mg/kg xylazine (Bayer Canada, Etobicoke, ON, Canada). For ECG and blood pressure monitoring, all MI >10 mm² (~10% MI size by circumference) were considered for the analyses. Only one rat had a MI <10 mm², and it was excluded from all analyses.

To obtain continuous electrocardiographic monitoring for arrhythmias, an hermetically sealed transmitter with a pair of helical wound flexible stainless steel wires (Data Sciences International) was implanted subcutaneously for continuous ECG recording. The positive lead was placed in a V4–V5 position (the xiphoid space and caudal to the rib cage) and attached to the underlying tissue to prevent migration; the negative lead was secured in the area of the right shoulder. The biopotential signal was digitized, amplified, and continuously emitted with the radiofrequency carrier.

To obtain continuous ambulatory blood pressure monitoring, an incision was made on the abdominal midline to permit access to the abdominal aorta. With the use of a bent needle as a catheter introducer, the blood pressure catheter was inserted upstream into the aorta. The body of the implant that contained the electronics for signal handling and radio-transmission was placed in the peritoneal cavity. The catheter insertion site was sealed, and the abdomen was closed. Once awakened after surgery, the rats were injected intramuscularly with 0.01 mg/kg buprenorphine HCl to reduce pain during recovery. The rats were then housed in an

![Fig. 1. Flow diagram of the various groups of rats according to the presence of myocardial infarction (MI) and treatment group. Oma, omapatrilat; H, hours; D, days; N, no. of animals.](http://ajpheart.physiology.org/)

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individual cage placed on a receiver that continuously captured the radiofrequency signal from the transmitter and converted it into a serial bit stream (Dataquest A.R.T.2.2, Data Sciences International). Ambient barometric pressure was also measured and subtracted from the telemetered pressure by data collection software to compensate for changes in atmospheric pressure.

Arrhythmia analysis. The observer classified all arrhythmic events on ambulatory electrocardiographic recordings according to the guidelines provided by the Lambeth Conventions (24). Ventricular tachycardia (VT) was defined as four or more consecutive ventricular premature beats (premature QRS complexes in relation to the P wave). Ventricular fibrillation (VF) was defined as a signal that changed from beat to beat in rate and morphology or a signal in which individual QRS deflections could not easily be distinguished from one another. The incidence and duration of arrhythmias were quantified as described by Curtis and Walker (7). As we did not measure individual premature beats, the scoring system for this study started at 2 and this score was given for one episode of spontaneously reverting VT or VF. A score of 3 was given for more than one episode of VT or VF or both with a total combined duration of <60 s. A score of 4 was given for VT or VF or both with a combined total duration of 60–119 s, 5 for VT or VF or both of a combined duration of >119 s, 6 for fatal VF starting at >15 min after occlusion, 7 for fatal VF starting at between 4 min and 14 min, 59 s after occlusion, 8 for fatal VF starting at between 1 min and 3 min, 59 s after occlusion, and 9 for fatal VF starting <1 min after occlusion. The average arrhythmia score was calculated for four post-MI time periods, 0–1 h, 1–6 h, 6–12 h, and 12–24 h. Rats that died during a time period were given a score of 9 for the following time periods.

Assessment of MI size. Rats dying <4 h after MI were considered to have had a large MI. Rats dying between 4 and 24 h or surviving 24 h after MI had their hearts removed for determination of infarct size by triphenyltetrazolium chloride (TTC). The LV was hand cut into four slices before fixation for more than one episode of VT or VF or both with a total combined duration of 5–119 s, 5 for VT or VF or both of a combined duration of >119 s, 6 for fatal VF starting at >15 min after occlusion, 7 for fatal VF starting at between 4 min and 14 min, 59 s after occlusion, 8 for fatal VF starting at between 1 min and 3 min, 59 s after occlusion, and 9 for fatal VF starting <1 min after occlusion. The average arrhythmia score was calculated for four post-MI time periods, 0–1 h, 1–6 h, 6–12 h, and 12–24 h. Rats that died during a time period were given a score of 9 for the following time periods.

Drug administration and experimental MI. One hundred fifty-six rats were chosen for long-term (38 days) follow up after MI (Fig. 1). These rats were randomly divided into the same two groups, omapatrilat (n = 82) and control (n = 74), 7 days before MI. Pre-, peri-, and post-MI drug administration and the experimental MI were identical to those of the 24-h protocol, except that rats had an echocardiogram at 30 days after MI and were treated for an additional 37 days after MI.

Echocardiographic measurements. Thirty days after MI, cardiac function and geometry were evaluated with an echocardiographic system equipped with a 15-MHz linear transducer (Acuson c526, Osiris Medical, Toronto, ON, Canada), as described previously (23). All studies were performed with rats anesthetized with 2% halothane (Halocarbon Laboratories, River Edge, NJ) by using a vaporizer for halothane (Harvard Apparatus, Quebec City, QC, Canada) and 0.2 l/min of oxygen. A comprehensive two-dimensional study was performed for the measurement of the LV circumference and areas in both systole and diastole. LV systolic diameter (LVSD), LV diastolic diameter (LVDD), and wall thickness were measured in the short-axis M mode with the right parasternal projection in a plane below the mitral valve and perpendicular to the LV. All primary measurements were traced manually and digitized by goal-directed, diagnostically driven software installed within the echocardiographic system. An average of 3 beats were used for the short-axis M-mode measurements.

Cardiac hemodynamic measurements. Thirty-eight days after MI, the rats were anesthetized with an intramuscular injection of a mixture of ketamine (50 mg/kg) and xylazine (10 mg/kg). The LV and right ventricular (RV) pressures were measured by a Millar Micro-Tip catheter transducer (Millar Instruments, Houston, TX) with a pressure sensor at the tip. The catheter was inserted into the right jugular vein and carotid artery and advanced to the RV and LV, respectively. Systolic and diastolic arterial pressures were measured in the carotid artery before the catheter was advanced to the LV. Ventricular pressures and the maximum rate of pressure rise (+dP/dt) and decline (−dP/dt) were both measured. The pressures were recorded on a Gould 2600S recorder (Gould, Cleveland, OH).

Morphological measurements. In rats surviving to 38 days, the heart was removed, rapidly rinsed in saline solution, and dissected into atria, RV, LV, septum, and scar. All portions of the heart, as well as the lungs, were then weighed individually. Animals were then classified by MI size according to scar surface as described in Assessment of MI size. Rats dying later than 24 h after MI but before hemodynamic monitoring had morphological assessment for classification of MI size by assessment of the percentage of LV circumference infarcted, as previously described (2), but were not used for other measurements except for survival. In rats surviving 38 days a large MI was defined as a LV scar surface of >35 mm² and a moderate MI as <35 mm². The surface area of a scar and the MI size by percentage of LV circumference infarcted are approximately the same in our experience (17).

Statistical Analysis

All data are expressed as means ± SE. Statistical significance was calculated with a Student’s unpaired t-test. Only probability values of P < 0.05 were accepted as statistically significant. Kaplan-Meier survival curves over the follow-up period were constructed and analyzed by the generalized Savage (Mantel-Cox) test.

RESULTS

Survival

24-h post-MI survival (n = 272). Survival of rats after MI is shown in Fig. 2. The sham-operated rats all survived. The overall survival 24 h after (moderate and large) MI in the control group (n = 73 deaths, 61 survivors) was 46%, which was less than in the omapatrilat group (n = 49 deaths, 72 survivors), of which 60% survived (P = 0.0378 vs. control).

24-h to 38-days post-MI survival (n = 106). Rats in the sham-operated groups all survived until the end of the study. For the control MI rats, 4 of 47 died (91% survival), similar to the omapatrilat group, where 2 of
47 rats with an MI died (96% survival; $P = 0.3914$ vs. control).

24-h Arrhythmia and Ambulatory Blood Pressure

**Incidence and duration of arrhythmias.** Average arrhythmia scores of rats with moderate and large MI 24 h after MI are shown in Fig. 3. No VT or VF was recorded during the 6-h baseline recording before coronary artery occlusion. During the first hour after MI, control rats had an average arrhythmia score of 4 compared with 3 for omapatrilat-treated rats ($P = 0.166$). From 1 to 6 h and from 6 to 12 h after MI, control rats had a greater arrhythmia score than omapatrilat-treated rats, 5 vs. 2 ($P = 0.008$) and 7 vs. 4 ($P = 0.028$), respectively. There was no difference in arrhythmia score 12–24 h after MI (6 for control vs. 5 for omapatrilat; $P = 0.826$).

**Ambulatory blood pressure.** Systolic and diastolic systemic blood pressures in rats with moderate and large MI during the first 24 h after MI are shown in Fig. 4. Treatment with omapatrilat (20 mg·kg$^{-1}$·day$^{-1}$) resulted in a significant decrease in systolic and diastolic arterial pressures before MI. This difference persisted throughout the experimental period in the sham-operated rats. During the post-MI period of monitoring, 0–24 h, blood pressure was significantly reduced in the control group. Treatment with omapatrilat did not result in a further decrease in blood pressure 0–24 h after MI.

**MI size.** Considering only rats in the 24-h protocol that survived the full 24 h, there was no difference in MI size between the control and omapatrilat-treated rats, 21 ± 2 vs. 20 ± 1 mm$^2$, respectively. If one then considers both survivors and rats dying between 4 and 24 h, rats receiving omapatrilat had smaller MIs, 36 ± 2 vs. 42 ± 2 mm$^2$ for control MI ($P = 0.034$).

38-Day Protocol

**Echocardiographic measurements.** Echocardiographic measurements at 38 days after MI are given in Table 1. In sham-operated rats, the only difference between control and omapatrilat groups was a decrease in posterior wall thickness in the omapatrilat group. Compared with sham-operated rats, control moderate MI rats had dilatation of the LV, with endocardial circumference in systole and diastole and LVDD and LVSD all increasing. Posterior wall thickness did not change, but anterior wall thickness (area of the MI) decreased. Omapatrilat-treated rats with a moderate MI had similar changes, except that the increase in LVDD was not significant compared with their omapatrilat-treated, sham-operated counterparts and posterior wall thickness decreased compared with moderate MI controls.

Compared with control sham-operated and moderate MI groups, control large MI rats had further LV dilatation, as reflected by an increase in endocardial circumference in systole and diastole and LVDD and LVSD. Anterior wall thickness resembled that of moderate MI, but posterior wall thickness decreased compared with that in sham-operated and moderate MI rats. Omapatrilat attenuated LV dilatation and reduced posterior wall thickness, but not anterior wall thickness, compared with control large MI rats.
systolic pressure (LVSP) and LV size were measured at 38 days after MI are shown in Table 2. In

Table 1. Echocardiographic measurements at 38 days after myocardial infarction

<table>
<thead>
<tr>
<th>n</th>
<th>LVDD, cm</th>
<th>LVSD, cm</th>
<th>Anterior Wall Thickness, mm</th>
<th>Posterior Wall Thickness, mm</th>
<th>Cir Diastolic Endocardium, cm</th>
<th>Cir Systole Endocardium, cm</th>
</tr>
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<tbody>
<tr>
<td>Sham operation</td>
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<tr>
<td>Control</td>
<td>6</td>
<td>0.87 ± 0.03</td>
<td>0.56 ± 0.06</td>
<td>1.44 ± 0.01</td>
<td>1.51 ± 0.01</td>
<td>2.71 ± 0.12</td>
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<tr>
<td>Omapatrilat</td>
<td>6</td>
<td>0.90 ± 0.02</td>
<td>0.65 ± 0.06</td>
<td>1.26 ± 0.01</td>
<td>1.85 ± 0.01*</td>
<td>2.61 ± 0.13</td>
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<td>Moderate MI</td>
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<tr>
<td>Control</td>
<td>13</td>
<td>1.06 ± 0.02†</td>
<td>0.89 ± 0.03†</td>
<td>1.02 ± 0.01†</td>
<td>1.45 ± 0.01</td>
<td>3.18 ± 0.08†</td>
</tr>
<tr>
<td>Omapatrilat</td>
<td>19</td>
<td>0.99 ± 0.02</td>
<td>0.83 ± 0.03†</td>
<td>1.07 ± 0.01†</td>
<td>1.24 ± 0.01*</td>
<td>3.13 ± 0.09†</td>
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<tr>
<td>Large MI</td>
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<tr>
<td>Control</td>
<td>30</td>
<td>1.18 ± 0.07‡‡</td>
<td>1.06 ± 0.09‡‡</td>
<td>0.99 ± 0.01†</td>
<td>1.36 ± 0.02‡‡</td>
<td>3.70 ± 0.28‡‡</td>
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<tr>
<td>Omapatrilat</td>
<td>26</td>
<td>1.06 ± 0.02‡‡</td>
<td>0.95 ± 0.02‡‡</td>
<td>0.93 ± 0.01‡‡</td>
<td>1.26 ± 0.01*</td>
<td>3.38 ± 0.07‡‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. LVDD, left ventricular (LV) diastolic dimension; LVSD, LV systolic dimension in short axis just below plane of mitral valve; Cir, circumference in 2 dimensions; MI, myocardial infarction. *P < 0.05 vs. control; †P < 0.05 vs. sham; ‡P < 0.05 vs. moderate MI.

Hemodynamic measurements. Hemodynamic measurements at 38 days after MI are shown in Table 2. In sham-operated rats, omapatrilat resulted in a decrease in both systolic and diastolic arterial pressure. LV systolic pressure (LVSP) and LV +dP/dt were also decreased. No other changes in the measured hemodynamic parameters were observed.

Compared with control sham-operated rats, control moderate MI rats had no change in the measured hemodynamic parameters, with the exception of LV +dP/dt, which was decreased, and RV end-diastolic pressure (RVEDP), which was increased. Compared with control moderate MI rats, omapatrilat resulted in a significant decrease in systolic and diastolic pressure, as well as a decrease in LVSP and RVEDP. Rats with moderate MIs treated with omapatrilat had no hemodynamic differences compared with their sham-operated counterparts.

As compared with control sham-operated, control large MI rats had an increase in LV end-diastolic pressure (LVEDP) and RV systolic pressure (RVSP) and a decrease in LVSP and in LV +dP/dt, all compatible with cardiac dysfunction. Omapatrilat treatment resulted in a further decrease in systolic and diastolic pressure, as well as in LVSP, LV +dP/dt, and RVSP. Omapatrilat treatment prevented all increase in RV pressures compared with sham-operated or moderate MI rats.

Morphological studies. Morphological parameters are given in Table 3. In sham rats, omapatrilat resulted in a decrease in total LV weight (septum + LV) to body weight ratio (TLW/BW) compared with the control group. No other change in the measured morphological parameters was observed in this category of rats.

Control moderate MI rats were not significantly different from their sham-operated counterparts, except for the presence of a LV scar. The other morphological differences between control and omapatrilat moderate MI rats were similar to those found in their sham-operated counterparts except for body weight, which was decreased.

Control large MI rats had an increase in scar surface and weight, in atrial weight-to-body weight ratio (AW/BW) and in RV weight-to-body weight ratio (RVW/BW) compared with their sham-operated and moderate MI counterparts. Also, compatible with lung congestion, they had an increase in wet lung weight-to-body weight ratio (Lung W/BW) compared with their sham-operated counterparts. Compared with control large MI rats, omapatrilat decreased body weight and TLW/BW (scar + septum + LV) similar to those in sham-operated and moderate MI rats. MI size and scar characteristics were similar, but RVW/BW, AW/BW, and Lung W/BW were all decreased compared with

Table 2. Hemodynamic measurements at 38 days after myocardial infarction

<table>
<thead>
<tr>
<th>n</th>
<th>HR, beats/min</th>
<th>SAP, mmHg</th>
<th>SAP, mmHg</th>
<th>LVSP, mmHg</th>
<th>LVEDP, mmHg</th>
<th>LV +dP/dt, mmHg</th>
<th>RVSP, mmHg</th>
<th>RVEDP, mmHg</th>
<th>RV +dP/dt, mmHg</th>
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<tr>
<td>Sham operation</td>
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<tr>
<td>Control</td>
<td>6</td>
<td>302 ± 10</td>
<td>116 ± 6.2*</td>
<td>86 ± 4.2</td>
<td>105 ± 6</td>
<td>8 ± 1</td>
<td>7,552 ± 510</td>
<td>27 ± 1</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Omapatrilat</td>
<td>6</td>
<td>311 ± 13</td>
<td>88 ± 2.9*</td>
<td>65 ± 3.6*</td>
<td>85 ± 5.9*</td>
<td>9 ± 1</td>
<td>5,705 ± 402*</td>
<td>26 ± 1</td>
<td>5 ± 1</td>
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<td>Moderate MI</td>
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<tr>
<td>Control</td>
<td>13</td>
<td>314 ± 11</td>
<td>117 ± 4.4</td>
<td>91 ± 3.6</td>
<td>100 ± 4</td>
<td>10 ± 1</td>
<td>5,889 ± 176*</td>
<td>28 ± 1</td>
<td>9 ± 1*</td>
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<tr>
<td>Omapatrilat</td>
<td>19</td>
<td>315 ± 12</td>
<td>96 ± 3.8*</td>
<td>72 ± 3.0*</td>
<td>82 ± 3.9*</td>
<td>9 ± 1</td>
<td>5,246 ± 236</td>
<td>25 ± 1</td>
<td>6 ± 1*</td>
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<td>Large MI</td>
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<tr>
<td>Control</td>
<td>30</td>
<td>357 ± 14</td>
<td>109 ± 2.7††</td>
<td>83 ± 2.1</td>
<td>86 ± 2.1†</td>
<td>13 ± 1††</td>
<td>4,835 ± 135††</td>
<td>32 ± 1†</td>
<td>9 ± 1†</td>
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<tr>
<td>Omapatrilat</td>
<td>26</td>
<td>368 ± 17</td>
<td>92 ± 3.4*</td>
<td>66 ± 2.6*</td>
<td>75 ± 2.8††</td>
<td>12 ± 1††</td>
<td>4,280 ± 129††</td>
<td>27 ± 1††</td>
<td>7 ± 1</td>
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</table>

Values are means ± SE. HR, heart rate; SAP, systolic arterial systemic pressure; DAP, diastolic arterial systemic pressure; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; LV +dP/dt, maximum rate of LV pressure development; RVSP, right ventricular (RV) systolic pressure; RVEDP, RV end-diastolic pressure; RV +dP/dt, maximum rate of RV pressure development. *P < 0.05 vs. control; †P < 0.05 vs. sham; ‡P < 0.05 vs. moderate MI.
those in control large MI rats, suggesting a decrease in hypertrophy and pulmonary congestion.

Considering only rats that survived 38 days with an MI, there was a statistically borderline decrease in MI size with omapatrilat (40 ± 2 vs. 50 ± 3 mm²; \(P = 0.0523\)). If one then considers both survivors and rats dying between 24 h and 38 days, the trend in favor of smaller MI with omapatrilat becomes significant (40 ± 2 vs. 49 ± 2 mm²; \(P = 0.0272\)).

**DISCUSSION**

In this study, pre-, peri-, and post-MI omapatrilat resulted in an improvement in survival. This improvement in survival was accompanied by a decrease in severity of ventricular arrhythmias, a decrease in MI size, and an improvement in LV remodeling and cardiac function. Interestingly, omapatrilat did not further reduce systemic arterial pressure during the first 24 h after MI. Together, these data would suggest that the effects of omapatrilat are beneficial in the acute and chronic post-MI periods.

Pre-, peri-, and post-MI omapatrilat improved survival. This improvement in survival was largely the result of better survival during the first 24 h of the MI but was sustained over the 38 days of the study. In a previous study of a relatively small number of rats (3), we found a similar beneficial effect of omapatrilat on 4-day post-MI survival and found this beneficial effect to be eliminated by the simultaneous administration of B₁ and B₂ BK receptor antagonists, suggesting that BK is involved in the cardioprotective effects of omapatrilat in this setting. In the present study, we confirmed these beneficial effects of omapatrilat in a larger number of rats, found that these early beneficial effects are sustained for a longer period after MI, and identified three mechanisms, which were likely interrelated, by which omapatrilat may have exerted these beneficial effects. These include a reduction in MI size, a reduction in ventricular arrhythmias, and an improvement of ventricular remodeling.

Omapatrilat reduced MI size, which clearly contributed to improved survival. Considering all rats, survivors and nonsurvivors 24 h after-MI, or rats that survived 38 days or died between 24 h and 38 days after MI, we found a reduction in MI size. Together, these findings would suggest that the early and sustained benefits of omapatrilat on survival were largely the result of a reduction in MI size. Although the reduction in MI size with omapatrilat was likely the convergence of a number of factors, our previous study indicating that blocking the effects of BK eliminated the benefits of omapatrilat on survival would suggest that BK may be involved (3). Intracoronary injection of BK in acute rabbit studies reduces infarct size to the same extent as the ACE inhibitor ramiprilat, whereas the BK B₂ receptor antagonist HOE-140 abolished the effect of ramiprilat (9). Compatible with this are experimental studies in arrhythmias and MI size were increased when BK was inhibited (15), studies of BK knockout mice demonstrating increased peri-MI mortality (25), and a clinical study in which an increase in plasma kallikrein levels was positively correlated with early survival after MI (10). Multiple mechanisms may be involved in BK-mediated protection against ischemic damage and include improved coronary and capillary nutritional flow (14, 16) and kinin-induced changes in cardiac metabolism, such as the preservation of high-energy-enriched phosphates and increased myocardial glucose uptake and use (14, 19).

Other potential mechanisms by which omapatrilat may have reduced MI size include hemodynamic and neurohumoral effects. To our surprise, during the first 24 h after MI, omapatrilat did not further reduce systemic arterial pressure. One possible explanation for this finding is that the dose of omapatrilat was inadequate. Against this is the reduction of systemic arterial pressure with omapatrilat before the MI and during studies done 38 days after MI. Nevertheless, during the first 24 h after MI, rats do not eat normally and may not have consumed enough omapatrilat to reach therapeutic levels. To counter this problem we gave rats omapatrilat (2 mg/kg ip) 4 h after MI and again the next morning. Although this was sufficient to reduce pressures in sham-operated rats, it may have been inadequate in rats with an MI. In any case, it would appear that, at least in the present study, the reduction in MI size with omapatrilat was not the result of a decrease in arterial pressure. Reduction in MI size could also have resulted from the direct neurohumoral effects of omapatrilat. These include a re-
duction in angiotensin II and an increase in natriuretic peptides (8, 20).

Omapatrilat reduced the severity of ventricular arrhythmias. This reduction in arrhythmias was largely confined to the period of 1–12 h after MI. At least part of this reduction in arrhythmias with omapatrilat resulted from its beneficial effect on MI size, but it may also have partially been the result of an antiarrhythmic effect of BK. Because BK may be involved in reducing MI size, it is difficult to determine what proportion of its antiarrhythmic effect is the result of a reduction in MI size and how much is the result of a direct antiarrhythmic effect. Nevertheless, there is a significant body of evidence suggesting that BK reduces peri-MI ventricular arrhythmias. Low doses of BK were shown to reduce ischemic arrhythmias and to improve myocardial electrical stability while not having an effect on coronary blood flow (14, 21, 22). BK also reduces the severity of ventricular arrhythmias induced by short-term occlusion–reperfusion, even before necrosis occurs (14, 22), and blockade of BK increases ventricular arrhythmias (15). Finally, BK appears to largely mediate the ACE inhibitor–induced reduction in norepinephrine and ventricular arrhythmias that occur during ventricular ischemia, as their protective effects are inhibited by blocking BK (6).

In this study, we also found that omapatrilat attenuated LV dilatation and helped preserve cardiac function 38 days after MI, a third mechanism that could have resulted in improved survival. The control large MI group had marked LV dilatation that was accompanied by a reduction in posterior wall thickness, suggesting some slippage of the cardiomyocytes in that area. Omapatrilat attenuated LV dilatation and hypertrophy in all groups. Because we did not assess LV remodeling 24 h after MI, we cannot be certain to what extent this contributed to the early benefits of omapatrilat. This improvement in ventricular remodeling was not accompanied by an improvement in LV function but was accompanied by a decrease in RVSP and a decrease in pulmonary wet weight suggesting a decrease in pulmonary congestion. This beneficial effect of omapatrilat did not result in improved survival from 24 h to 38 days after MI. The major reason for this is the small number of deaths in the control group (4 of 47) during this period, making our study woefully underpowered to determine a difference in survival. It is possible that with a longer follow-up, the beneficial effects of omapatrilat on LV remodeling would have resulted in improved survival. In support of this is the late survival benefit with the ACE inhibitor captopril in the survival and ventricular enlargement study (SAVE; Ref. 18).

In conclusion, this study indicates that pre-, peri- and post-MI treatment with the VPI omapatrilat improves survival. Along with improved survival, omapatrilat reduces MI size, decreases ventricular arrhythmias and results in improved LV remodeling and cardiac function. The results of this study, combined with our previous work, would suggest that pre-, peri- and/or post-MI VPI omapatrilat is beneficial in rats.

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