Low-dose simvastatin improves survival and ventricular function via eNOS in congestive heart failure

James J. M. Greer,1 Aman K. Kakkar,2 John W. Elrod,3 Lewis J. Watson,4 Steven P. Jones,4 and David J. Lefer3

1Department of Molecular and Cellular Physiology, 2Division of Cardiology, Louisiana State University Health Sciences Center, Shreveport, Louisiana; 3Division of Cardiology and Department of Pathology, Albert Einstein College of Medicine, Bronx, New York; and 4Institute of Molecular Cardiology, University of Louisville, Louisville, Kentucky

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Greer, James J. M., Aman K. Kakkar, John W. Elrod, Lewis J. Watson, Steven P. Jones, and David J. Lefer. Low-dose simvastatin improves survival and ventricular function via eNOS in congestive heart failure. Am J Physiol Heart Circ Physiol 291: H2743–H2751, 2006. First published July 14, 2006; doi:10.1152/ajpheart.00347.2006.—3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors increase endothelial nitric oxide synthase (eNOS) activity by multiple mechanisms. We previously reported that genetic overexpression of eNOS improves survival and cardiac function in congestive heart failure (CHF). In the present study, we tested the hypothesis that low-dose treatment with an "inactive lactone prodrug form. Simvastatin was administered to mice by intraperitoneal injection at a dose of 0.25 mg/kg 2 h after myocardial infarction (MI) and daily (0.25 mg/kg) for 7 days, followed by 21 days of administration every other day for a total duration of 28 days. Myocardial infarct size was not reduced by simvastatin therapy (P not significant between groups). Simvastatin treatment did significantly (P < 0.05) improve survival (45%) compared with vehicle treatment (25%). In addition, simvastatin treatment significantly improved (P < 0.01) left ventricular function and significantly (P < 0.01) abrogated cardiac hypertrophy and pulmonary edema compared with vehicle treatment. The protective effects of simvastatin were abrogated by delayed initiation of treatment or genetic ablation of eNOS. In conclusion, low-dose simvastatin therapy significantly improves survival and cardiac function and reduces both cardiac hypertrophy and pulmonary edema via an eNOS-dependent mechanism in a murine model of CHF.

MATERIALS AND METHODS

Mice

Eight- to ten-week-old male C57BL/6J mice utilized in the study were obtained from Jackson Laboratory (Bar Harbor, ME). In addition, eNOS−/− mice were originally donated by Dr. Paul Huang (Massachusetts General Hospital). The eNOS−/− mice were back crossed onto the C57BL/6J background for at least 15 generations and generated in our breeding colony. The eNOS−/− mice that were used were 8–10 wk of age.

Animals

All animals received humane care in compliance with the “Principals of Laboratory Animal Care” formulated by the National Society of Medical Research and the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Publication No. 85-23, Revised 1996). The experimental protocol for the present study was reviewed and approved by the Institutional Animal Care and Use Committee of the Albert Einstein College of Medicine.

Simvastatin Preparation

Preparation. Pure simvastatin powder was obtained from Merck (Rahway, NJ) in the inactive lactone prodrug form. Simvastatin was

3-HYDROXY-3-METHYLGLUTARYL COENZYMES A (HMG COA) REDUCTASE INHIBITORS (i.e., statins) reduce plasma cholesterol levels by inhibiting the rate-limiting step in cholesterol biosynthesis. The cholesterol-lowering effects of statins and their ability to reduce morbidity and mortality in cardiovascular disease have been proven in multiple clinical trials (23a, 24). Although reductions in serum lipids and plaque stabilization may account for part of the clinical benefit of statins (18, 19), additional clinical evidence suggests mechanisms independent of diminishing hypercholesterolemia (22). A growing body of evidence implicates improvements in endothelial function and endothelium-derived nitric oxide (NO) as potential mediators (6, 17).

It is now widely accepted that statins increase NO bioavailability via activation of endothelial nitric oxide synthase (eNOS). Indeed, several groups have identified multiple molecular mechanisms for statin-mediated eNOS activation (26). Specifically, statins have been shown to increase eNOS mRNA half-life by inhibition of Rho (15) and phosphorylation of eNOS protein by activation of the phosphatidylinositol 3-kinase/Akt pathway (13). Statin-mediated modulation of eNOS expression and activity may prove beneficial in deterring the progression of cardiovascular diseases, especially congestive heart failure (CHF). Endothelial dysfunction leads to compromised eNOS activity in animal models and humans with CHF (2, 4, 5). A previous study of CHF in mice demonstrated that genetic overexpression of eNOS preserved cardiac performance and improved survival (11). Such results suggest that pharmacological approaches to improve eNOS activity would exert protective effects in the setting of CHF.

We hypothesized that HMG CoA reductase inhibition with a low dose of simvastatin would attenuate the severity of CHF via induction of eNOS. We induced CHF in mice by permanent ligation of the left coronary artery (LCA) and evaluated survival, left ventricular (LV) function, cardiac hypertrophy, and pulmonary edema.
Simvastatin (0.25 mg/kg) was administered intraperitoneally at 2 h after left coronary artery (LCA) ligation. Additional simvastatin doses (0.25 mg/kg) were administered every day (QD) for 6 days and then every other day (QOD) for 21 days. B: heart failure protocol for mice receiving delayed simvastatin therapy. Simvastatin therapy (0.25 mg/kg) was initiated at 48 h after LCA occlusion. Subsequent doses of simvastatin (0.25 mg/kg) were administered QD for 4 days and then QOD for the final 21 days of the experimental protocol. LV, left ventricle.
Table 1. Circulating lipid levels in vehicle and simvastatin treated mice

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Total Cholesterol, mg/dl</th>
<th>HDL, mg/dl</th>
<th>LDL, mg/dl</th>
<th>Triglycerides, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>9</td>
<td>72 ± 4</td>
<td>45 ± 5</td>
<td>9 ± 2</td>
<td>89 ± 4</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>10</td>
<td>78 ± 3</td>
<td>55 ± 3</td>
<td>9 ± 1</td>
<td>76 ± 10</td>
</tr>
</tbody>
</table>

Values are means ± SE. Serum lipids were measured at 28 days after daily administration of simvastatin (0.25 mg/kg) in sham-operated mice. No significant differences were observed between the vehicle and simvastatin groups.

(12). Mice were lightly anesthetized with pentobarbital sodium (40 mg/kg). Ventricular parameters were measured by the leading-edge technique. M-mode (sweep speed = 200 mm/s) echocardiograms were captured from parasternal and short- and long-axis two-dimensional views of the LV at the midpapillary level. Left ventricular end-diastolic diameters (LVEDD), left ventricular end-systolic diameters (LVESD), aortic diameter, aortic velocity time integral, and heart rate were measured at baseline and at 28 days after permanent occlusion of the LCA. LV percent fractional shortening (FS) was calculated according to the following equation: 

\[ \text{LVFS} = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}} \times 100 \]

Stroke volume was calculated from the product of the aortic cross-sectional area [(aortic diameter/2)^2 × π] and the aortic velocity time integral. All data were calculated from 10 cardiac cycles per experiment.

Pulmonary Edema

Lungs from mice subjected to myocardial infarction or sham operation were excised after 28 days to determine pulmonary fluid accumulation. Excised lungs were immediately weighed (wet weight) and placed in a drying oven (Econotherm Laboratory Oven, Precision Systems, Natick, MA) for 7 days at 40°C. Lungs were weighed after the drying procedure (dry weight), and the difference between wet and dry weights represented pulmonary fluid.

Cholesterol and Triglyceride Determinations

Serum was collected after 28 days from an additional group of sham-operated mice randomized to receive simvastatin (0.25 mg/kg; n = 10) or vehicle (n = 9) injections (QOD) for 28 days to determine cholesterol and triglyceride content. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations were assessed by Christus Schumpert Health System Pathology Laboratory, using the Dimension Clinical Chemistry System (Dade Behring, Deerfield, Illinois) and Flex reagents.

Liver Enzyme Determinations

Serum was collected at 28 days postsurgery from sham-operated mice (n = 8 per group) randomized to injections of simvastatin (0.25 mg/kg QOD) or saline vehicle.

Serum samples were analyzed for aspartate aminotransferase and alanine aminotransferase with a spectrophotometric method (Sigma, St. Louis, MO) to assess the effects of prolonged simvastatin therapy on hepatic function.

Myocardial eNOS Western Blotting

Mice (n = 8 per group) were subjected to the immediate simvastatin therapy protocol (Fig. 1A) in the absence of LCA occlusion. Cardiac lysates were centrifuged to remove any particulate, and protein concentration of the cleared lysate was measured by the Bio-Rad DC protein assay. Equal amounts of protein were loaded into each lane and separated on a 6% polyacrylamide gel. Protein was transferred to polyvinylidene difluoride overnight at 30 V and then blocked in 5% milk-Tris-buffered saline-Tween 20 (TBST) at room temperature for 3 h. Membranes were washed three times with TBST and then incubated with mouse anti-eNOS (1:4,000) (BD Transduction Labs) in 5% BSA TBST overnight at 4°C. Membranes were then washed three times with TBST and then incubated with horseradish peroxidase-linked anti-mouse secondary antibody (Amersham) at 1:2,000 in 5% BSA-TBST at room temperature for 3 h. Membranes were then washed three times with TBST, incubated with enhanced chemiluminescence reagents (Amersham), and then exposed to film. Densitometric analysis was performed using NIH Image software.

Cardiac Tissue Nitrate and Nitrite Levels

Additional mice (n = 8 per group) were subjected to the immediate simvastatin therapy protocol (Fig. 1A) in the absence of LCA occlusion. At 28 days after baseline, cardiac tissue homogenates were centrifuged for 20 min at 12,500 g, and the supernatants were normalized to the total protein content according to the Bradford assay. Each sample was then filtered to remove proteins, and resultant cleared homogenates were spectrophotometrically analyzed for nitrate and nitrite (NOx) levels using a commercially available system (NO quantitation kit from Active Motif). Samples were analyzed in triplicate, and absorbance was measured at a wavelength of 540 ± 2 nm on a Multiskan Spectrum (Thermo Electron) plate reader controlled by SkanIt Software (version 2.1).

Statistical Analysis

Data were analyzed by Student’s unpaired t-test or ANOVA with Bonferroni post hoc analysis using StatView (SAS Institute, Cary, NC) software. Data are reported as means ± SE, with differences accepted as significant at P < 0.05.

RESULTS

Circulating Lipid Levels

Simvastatin treatment did not alter circulating lipid levels in sham-operated mice treated with simvastatin (n = 10) for 28 days (Table 1). No changes were observed in total cholesterol, low-density lipoprotein cholesterol, or high-density lipoprotein cholesterol levels compared with mice receiving saline vehicle (n = 9). Similarly, there were no significant changes in serum triglyceride levels between the simvastatin-treated mice and mice receiving saline vehicle (Table 1).

Liver Enzymes

Simvastatin therapy exerted no significant changes in hepatic enzyme levels in mice after the 28-day experimental protocol (Table 2). Liver enzyme levels in sham-operated mice receiving simvastatin (n = 8) were similar to levels in mice receiving vehicle (n = 8).

Circulating Simvastatin Levels

Studies were performed in sham-operated control (n = 5 per group) mice to determine the circulating levels of simvastatin
in mice treated with simvastatin (0.25 mg/kg QD) for 7 days followed by simvastatin (0.25 mg/kg QOD) for 21 days. Plasma simvastatin was undetectable in animals receiving saline vehicle and 13.4 ± 5.94 ng/ml in mice receiving 0.25 mg/kg simvastatin QOD for 28 days.

**Myocardial Infarct Size**

The extent of myocardial infarction was examined in simvastatin-treated (n = 8) and saline vehicle control (n = 8) mice at 48 h after permanent LCA occlusion (Fig. 2A). The area-at-risk per LV was 44.2 ± 2.6% in simvastatin-treated and 43.0 ± 4.6% in vehicle mice (P = not significant between groups). The infarct size per LV was also similar in both groups, with 41.7 ± 1.2% in the simvastatin group and 38.6 ± 3.6% in the saline vehicle group (P = not significant between groups). In addition, infarct size per area at risk was 92.8 ± 2.3% in the simvastatin group, which was similar (P = not significant between groups) to that observed in the saline vehicle group (90.8 ± 4.6%).

Myocardial infarct size was also determined histologically at 28 days after permanent coronary artery ligation (Fig. 2B). Myocardial infarct size per LV was not significantly different between the saline vehicle and simvastatin groups.

**Survival**

Both saline-treated mice and simvastatin-treated mice subjected to myocardial infarction exhibited significant (P < 0.05) mortality compared with sham-operated mice receiving saline vehicle (Fig. 3). Myocardial infarcted mice receiving saline vehicle experienced an overall survival rate of 25% during the 28-day protocol compared with mice treated with simvastatin, which resulted in 45% survival. This represents a 45% improvement in survival compared with the saline vehicle control group (P < 0.05 between groups). In contrast to immediate treatment with simvastatin, delayed treatment (48 h after LCA occlusion) of simvastatin did not improve survival (26%, n = 19) compared with the saline vehicle group (P = not significant between groups).

**LV Dimensions**

Permanent ligation of the LCA resulted in significant LV dilatation in mice receiving saline vehicle (Fig. 4A). However, simvastatin treatment of mice (QD for 7 days and QOD for 21 days) subjected to myocardial infarction significantly attenuated LV dilatation in both diastole and systole at 28 days after myocardial infarction compared with vehicle-treated controls (P < 0.01 between groups). In fact, LV dimensions in simvastatin-treated mice were similar to those observed in sham-operated control mice (P = not significant between groups).

**LV Function**

LV function data in sham, myocardial infarction + vehicle, and myocardial infarction + simvastatin mice 28 days after myocardial infarction are presented in Fig. 4B. Fractional shortening was significantly (P < 0.01) attenuated at 28 days after myocardial infarction in saline vehicle mice (18.6 ± 1.8%) compared with sham-operated mice (31.8 ± 2.3%).

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Fig. 2. Myocardial infarction. A: myocardial infarct size measured at 48 h after coronary artery occlusion in vehicle-treated (n = 8) and simvastatin-treated (n = 8) mice. Simvastatin (0.25 mg/kg) did not alter the extent of MI (INF) per area-at-risk (AAR) or the infarct size per LV. The area-at-risk per LV was similar in both study groups. B: myocardial infarct size per LV measured histologically in vehicle-treated (n = 5) and simvastatin-treated (n = 4) mice at 28 days after MI. Simvastatin failed to alter the extent of myocardial infarct size at 28 days postinfarction. NS, not significant.

Fig. 3. Survival in wild-type mice. A: Kaplan-Meier survival curve in vehicle-treated sham (n = 12) and vehicle-treated myocardial infarcted wild-type mice (n = 64) as well as sham-operated (n = 12) and wild-type myocardial-infarcted mice (n = 49) treated with simvastatin (0.25 mg/kg) 7 days QD followed by 21 days of QOD treatment. Both saline- and simvastatin-treated mice exhibited significant reductions in survival compared with sham-operated animals (P < 0.01 vs. sham group). Simvastatin treatment improved survival in mice subjected to MI by 45% (P < 0.01 vs. saline group).
Mice receiving simvastatin displayed fractional shortening values (26.2 ± 2.1%) that were significantly improved over vehicle-treated myocardial infarction mice (P < 0.01 between groups).

Assessment of LV ejection fraction (EF) revealed similar findings in that vehicle-treated myocardial infarcted mice demonstrated a significant (P < 0.01 vs. sham) reduction in EF at 28 days after myocardial infarction (37.8 ± 4.3%) compared with sham-operated mice (65.4 ± 2.3%) (Fig. 4B). Mice receiving simvastatin exhibited a significant (P < 0.01) improvement in EF (58.9 ± 6.0%) compared with mice receiving vehicle and demonstrated recovery of EF that approached the values observed in sham-operated controls (Fig. 4B). No significant differences in EF were observed at baseline between the study groups.

**Cardiac Hypertrophy**

Permanent LCA ligation resulted in significant (P < 0.01) increases in the heart-to-body weight ratio at 28 days after myocardial infarction in both vehicle (9.2 ± 1.4 mg/g) and simvastatin-treated mice (6.1 ± 0.32 mg/g) compared with sham-operated controls (4.6 ± 0.13 mg/g), indicative of cardiac hypertrophy (Fig. 5A). However, simvastatin therapy significantly attenuated the degree of hypertrophy compared with the vehicle group (P < 0.05 between study groups).

Analysis of cardiac myocyte size (Fig. 5B) revealed a significant (P < 0.05) reduction in cross-sectional ratio (myocyte to nucleus) in simvastatin-treated mice at 28 days after myocardial infarction compared with mice receiving saline vehicle.

**Pulmonary Edema**

Examination of pulmonary fluid (Fig. 6) in mice subjected to myocardial infarction and treated with saline vehicle revealed significant (P < 0.01) pulmonary edema (128.4 ± 14 mg) compared with sham-operated control mice (96.1 ± 2.7 mg).
Interestingly, mice receiving simvastatin displayed no appreciable pulmonary edema (103.8 ± 6 mg) after myocardial infarction compared with sham-operated mice (P = not significant between groups).

Survival in eNOS−/− Mice

eNOS−/− mice subjected to myocardial infarction demonstrated significant (P < 0.01) decreases in survival (Fig. 7A) in the saline vehicle group (32%) compared with eNOS−/− sham-operated mice (100%). However, simvastatin treatment failed to improve survival (28%) at 28 days after myocardial infarction compared in eNOS−/− mice (P = not significant between groups).

Cardiac Dimensions and LV Function in eNOS−/− Mice

Data for cardiac dimensions and LV function in eNOS−/− subjected to myocardial infarction and subsequent heart failure are presented in Fig. 7, B–E. Simvastatin treatment failed to prevent ventricular dilatation or dysfunction in eNOS−/− mice in the setting of heart failure.
Simvastatin did not reduce cardiac hypertrophy in eNOS−/− mice (0.25 mg/kg) compared with mice receiving saline. Simvastatin treatment also exerted beneficial effects on LV function. All of the beneficial effects of simvastatin therapy were observed in the absence of reductions in circulating lipid levels or elevations in liver enzymes. Simvastatin failed to exert favorable effects in eNOS−/− mice subjected to heart failure, suggesting requirement of eNOS. We also determined that, although simvastatin treatment did not alter myocardial eNOS protein levels, there was an increase in NO metabolites (i.e., NOx), suggesting an increase in NO activity and NO bioavailability. These data provide additional insight into the pleiotropic effects of statins regarding hypcholesterolemic-independent effects in cardiovascular disease.

The pleiotropic effects of statins have been investigated in multiple diseases. The CARE trial (22) provided evidence of cardiovascular benefits despite cholesterol levels in the normal range before statin treatment. Furthermore, multiple experimental studies have demonstrated reductions in myocardial infarct size in the absence of cholesterol lowering (16, 26). Recently, Jones et al. (10) demonstrated that statin-mediated protection against myocardial ischemia-reperfusion injury was eNOS dependent because eNOS−/− mice treated with rosuvastatin displayed no reduction in infarct size. In addition, Endres et al. (7) demonstrated that the protection afforded by statins in stroke was dependent on the presence and activation of eNOS. The present study adds to a compelling and growing body of evidence that supports the lipid-lowering independent cardiovascular benefits of statin treatment.

Recent studies investigated the effects of prolonged statin treatment in more chronic cardiovascular diseases. Patel et al. (20) found that simvastatin induced regression of hypertrophy and fibrosis as well as improved cardiac function in a rabbit model of cardiac hypertrophy induced by overexpression of the β-myosin heavy chain-Q403. In addition, in a rat infarct model of heart failure, Bauersachs et al. (3) reported improvements in LV developed pressure and dP/dt following cerivastatin treatment. These improvements were attributed to favorable remodeling after myocardial infarction as reduced gene levels of β-myosin heavy chain and collagen I were observed (3). Another heart failure study by Hayashidani et al. (8) reported improved survival, LV systolic and diastolic dimensions, and LV fractional shortening after fluvastatin treatment at a dose of 10 mg·kg−1·day−1. Despite the use of a very high dose of fluvastatin in their study, eNOS protein expression was not increased at 28 days postinfarction. The authors suggested that fluvastatin protected without augmenting eNOS protein levels. However, the authors failed to consider changes in the serine 1177 phosphorylation status or increased activity of eNOS. Finally, Landmesser et al. (14) investigated the role of statin therapy with atorvastatin (50 mg·kg−1·day−1) in a mouse model of ischemia-induced heart failure. The authors reported improved survival and cardiac function. In addition, a loss of these protective effects in eNOS−/− mice was also observed. The Landmesser study suggests that statins mediate improved survival by favorable remodeling and by the proangiogenic effects of atorvastatin in the setting of CHF.

**Cardiac Hypertrophy in eNOS−/− Mice**

Analyses of heart-to-body weight ratios in eNOS−/− mice subjected to myocardial infarction revealed similar results in vehicle (7.9 ± 0.3 mg/g) and simvastatin-treated (8.2 ± 0.7 mg/g) groups (P = not significant between groups). Thus simvastatin did not reduce cardiac hypertrophy in eNOS−/− mice at 28 days after myocardial infarction.

**Pulmonary Edema in eNOS−/− Mice**

In eNOS−/− mice receiving saline vehicle, pulmonary fluid accumulation was 139.4 ± 14 mg compared with 126.8 ± 7 mg in eNOS−/− mice treated with simvastatin (P = not significant between study groups). Thus simvastatin therapy failed to ameliorate the severity of pulmonary edema in the absence of eNOS following myocardial infarction.

**Cardiac eNOS Protein Levels**

Myocardial eNOS protein levels were measured in sham-operated animals that received either saline vehicle or simvastatin therapy for 28 days (Fig. 8). There was no change in cardiac eNOS protein levels in animals receiving simvastatin (0.25 mg/kg) compared with vehicle animals.

**Cardiac Tissue NOx Levels**

Myocardial tissue NOx levels were determined in sham-operated animals that received simvastatin (0.25 mg/kg) or saline vehicle for 28 days (Fig. 8B). Simvastatin therapy resulted in a significant (P < 0.05) increase in total NOx levels.

**DISCUSSION**

Data from this study clearly demonstrate that low-dose simvastatin therapy significantly retards the progression of CHF in mice after acute myocardial infarction. The key finding in this study is that simvastatin administered within hours of infarction improved survival by 45%. In addition, LV dilation and hypertrophy were markedly improved in simvastatin-treated mice compared with mice receiving saline. Simvastatin treatment also exerted beneficial effects on LV function. All of the beneficial effects of simvastatin therapy were observed in the absence of reductions in circulating lipid levels or elevations in liver enzymes. Simvastatin failed to exert favorable effects in eNOS−/− mice subjected to heart failure, suggesting requirement of eNOS. We also determined that, although simvastatin treatment did not alter myocardial eNOS protein levels, there was an increase in NO metabolites (i.e., NOx), suggesting an increase in NO activity and NO bioavailability. These data provide additional insight into the pleiotropic effects of statins regarding hypcholesterolemic-independent effects in cardiovascular disease.

Cardiac eNOS protein as determined with Western blot analysis at 28 days in vehicle- and simvastatin-treated (0.25 mg/kg) mice in sham-operated controls. No differences were observed in total eNOS protein levels. In eNOS−/− mice subjected to myocardial infarction revealed similar results in vehicle (7.9 ± 0.3 mg/g) and simvastatin-treated (8.2 ± 0.7 mg/g) groups (P = not significant between groups). Thus simvastatin did not reduce cardiac hypertrophy in eNOS−/− mice at 28 days after myocardial infarction.

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Fluvastatin has been show to inhibit matrix metalloproteinase-1 expression in human vascular endothelial cells (9), which could possibly be applied to the myocardium itself because it plays a critical role in the development of heart failure. It has been shown that LV hypertrophy can be attenuated in a mouse model of myocardial infarction by matrix metalloproteinase-1 inhibition (23).

Statin-mediated angiogenesis is now widely accepted as multiple studies have shown neovascularization from statin administration (13, 25). The study by Kureishi et al. (13) demonstrates that statin-mediated angiogenesis occurs via Akt activation of eNOS and suggests that phosphorylation of eNOS, rather than upregulation of protein expression, is responsible for the proangiogenic effects of statins. The angiogenic effects of statin administration may play a critical role in the improvements of survival and LV function observed in the present study. Recently, endothelial progenitor cell mobilization has been shown to be dependent on NO (1). Increased NO bioavailability as a result of statin therapy may have increased circulating endothelial progenitor cells in our model of heart failure, resulting in the growth of new blood vessels in the myocardium.

The present study convincingly demonstrates that low-dose (i.e., 0.25 mg·kg⁻¹·day⁻¹) simvastatin treatment initiated after coronary occlusion significantly improves survival, preserves cardiac function, and reduces pulmonary edema. Previous studies of statin therapy in the setting of CHF have been focused on very high dosages of statins, ranging from 10 to 50 mg/kg, in rodents. The highest dosages of statins that are responsible for the proangiogenic effects of statins. The angiogenic effects of statin administration may play a critical role in the improvements of survival and LV function observed in the present study. Recently, endothelial progenitor cell mobilization has been shown to be dependent on NO (1). Increased NO bioavailability as a result of statin therapy may have increased circulating endothelial progenitor cells in our model of heart failure, resulting in the growth of new blood vessels in the myocardium.

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GRANTS

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