Simvastatin improves left ventricular function after myocardial infarction in hypercholesterolemic rabbits by anti-inflammatory effects

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Received 6 February 2006; received in revised form 14 August 2006; accepted 21 August 2006
Available online 30 August 2006
Time for primary review 29 days

Abstract

Objectives: Hypercholesterolemia contributes to coronary artery disease progression but little is known about its effect on left ventricular (LV) function after myocardial infarction (MI). The aim of this study was to investigate the effects of hypercholesterolemia and statin treatment in rabbits with experimental MI.

Methods and results: New Zealand White rabbits on a normal or cholesterol-rich diet for 4 weeks, underwent permanent coronary artery ligation. Starting on the first day post-MI rabbits were treated with either placebo or simvastatin (5 mg/kg/day) for 9 weeks. Hypercholesterolemia itself did not affect LV function in sham-operated animals but further impaired LV systolic (dP/dt max -42%) and diastolic (dP/dt min -47%) function in MI rabbits on placebo. Simvastatin treatment not only prevented deterioration of LV function associated with hypercholesterolemia but improved LV function (dP/dt max +130%; dP/dt min +144%, P<0.05). Simvastatin also attenuated the depression of LV function in normocholesterolemic MI rabbits (dP/dt max +46%; dP/dt min +53%, P<0.05). Hypercholesterolemia in MI rabbits coincided with a significant increase in C-reactive protein levels (marker of inflammation) and Rac1-GTPase activity (marker of oxidative stress), and a reduction in cardiac sarcoplasmic-reticulum calcium ATPase-2 expression and endothelial nitric oxide synthase protein phosphorylation, all of which were normalised by simvastatin treatment. Elevated serum cholesterol levels were only partially reduced by simvastatin.

Conclusions: Hypercholesterolemia further impaired the depressed LV function in rabbits post-MI. Statin treatment reversed this effect, and conferred additional protection, as in normocholesterolemic animals. Our study suggests that anti-inflammatory and anti-oxidative effects of simvastatin substantially contribute to its beneficial effects on cardiac function after MI.

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Keywords: Infarction; Heart failure; Cholesterol; Statins; Inflammation

1. Introduction

Myocardial infarction (MI) represents the most important cause for the development of cardiac failure [1]. Elevated cholesterol levels are one of the major underlying risk factors for coronary artery disease, however, there is only limited information available regarding the direct effect of hypercholesterolemia on ventricular function [2,3]. While left ventricular (LV) myocytes isolated from cholesterol fed rabbits showed a reduction in systolic and diastolic function [3], no reliable data are available from in vivo investigations. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (the statins) such as simvastatin have favorable effects on the pathogenesis of atherosclerosis, resulting in lower cardiovascular morbidity and mortality in patients with a wide range of cholesterol levels [4–6]. Interestingly, statin treatment reduces cardiovascular events even in the absence of elevated baseline cholesterol levels;
effects that can also be observed early after acute coronary syndromes suggesting that these compounds may exert beneficial effects that are independent from their effects on cholesterol lowering. Indeed, statins increase the expression of the endothelial nitric oxide synthase (eNOS) and attenuate superoxide anion (O$_{2}^-$) formation leading to improved endothelial function [7–9]. In addition, markers of inflammation such as C-reactive protein (CRP) and tumor necrosis factor-α (TNFα) are decreased by statins in patients with coronary artery disease and hypercholesterolemia [10–12].

There is also some evidence that statin therapy reduces the risk for the development of heart failure. Indeed, in the Scandinavian Simvastatin Survival Study (4S) fewer patients on simvastatin developed heart failure than on placebo; this was related to a reduction in recurrent MI [13]. Furthermore, statin treatment attenuated angiotensin II-induced cardiac myocyte hypertrophy, which is probably mediated by reactive oxygen species (ROS) [14]. Indeed, ROS are associated with reduced cardiac function and correlate with the severity of CHF [15,16]. In animal models of heart failure after MI, statins attenuated LV remodeling and improved cardiac function [17,18], however, to which extent these effects can be attributed to reduced cholesterol levels is unclear.

The aim of the present study was to elucidate the effect of hypercholesterolemia on LV remodeling and function in rabbits with and without heart failure after MI. Plasma CRP levels as well as eNOS and sarcoplasmic-reticulum calcium ATPase (SERCA)-2 protein expression, and Rac1-GTPase activity, a regulator of the NADPH oxidase [9], were assessed in LV myocardium. Furthermore, we investigated the effect of simvastatin on LV remodeling and function in normo- and hypercholesterolemic rabbits with MI, and assessed its effect on plasma cholesterol, inflammation and oxidative stress.

2. Methods

2.1. Study design

Male New Zealand rabbits (2.5–3.1 kg, n=50) were used for all experiments. Animals were housed in separate cages in an environmentally controlled facility and were maintained on standard rabbit chow and given water ad libitum. Four weeks prior to MI animals were divided into 2 groups receiving either a standard rabbit chow (n=25) or an atherogenic diet (0.25% cholesterol, 3% coconut oil; n=25). Lipid levels significantly increase within the first 20 days of atherogenic diet [19]. The investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996).

2.2. Induction of myocardial infarction

Rabbits were anesthetized with propofol (Astra Zeneca, Wedel, Germany; 25 mg kg$^{-1}$ i.v.), intubated and mechanically ventilated with oxygen and 5% sevo-flurane (Abbott, Wiesbaden, Germany). Animals (n=50) underwent a thoracotomy in the fourth intercostal space and the pericardium was opened. In 35 animals, a large branch of the LCx was ligated with a prolene suture whereas 15 animals underwent a sham operation. Ventricular fibrillation occurred in approximately 60% of ligated animals. Defibrillation was undertaken with a 2.0 J epicardial shock. After surgery all rabbits received oxytetracycline hydrochlorid (Pfizer, Karlsruhe, Germany; 15 mg kg$^{-1}$ s.c.) and metamizol (Hoechst, Unterschleissheim, Germany; 20 mg kg$^{-1}$ i.m.) for two days to limit post-surgical pain and infection. On the first day post-MI or sham operation, animals were randomized to receive either placebo chow (n=15) or simvastatin (5 mg/kg via chow; n=16) for 9 weeks. The dosages required for significant treatment effects in rabbits are in general much higher than that given to men. This dosage was found to decrease total cholesterol levels in rabbits to the same extent as the standard dose in humans and is far below toxic dosages [20,21]. In rabbit models of atherosclerosis, hypertrophic cardiomyopathy and heart failure, this dosage was proved to be effective, while lower dosages were not [22–24]. The experimental protocol consisted of six groups of rabbits: normal diet Sham (n=7), normal diet MI/Control (n=8); normal diet MI/Simvastatin (n=8); atherogenic diet Sham (n=7); atherogenic diet MI/Control (n=8) and atherogenic diet MI/simvastatin (n=8).

2.3. Echocardiographic assessment of the LV

In vivo transthoracic echocardiography of the LV was performed at baseline as well as 3 and 8 weeks after surgery in all groups using a 5–8 MHz linear array transducer interfaced with a ATL 2000 [25]. Measurements of LV size and function were obtained in all animals. Rabbits were lightly anesthetized with a mixture (0.5 ml/kg of body weight IM) of ketamine (50 mg/kg) and rompun (10 mg/kg). M-mode echocardiograms were captured from the parasternal, short axis view. Posterior wall thickness (PWTh), left ventricular end-diastolic and end-systolic diameter (EDD and ESD) were assessed at the midpapillary level. Two-dimensional echocardiography was performed in the parasternal long axis view to measure the left ventricular end diastolic area (EDA). Fractional shortening (FS, %) was calculated as EF= (EDD – ESD)/EDD × 100. Velocity of circumferential fiber shortening (vcf, circ/s) was calculated as Vcf=((EDD− ESD) × 1000/EDD × LVET)/heart rate. Left ventricular outflow ejection time (LVET) was taken from a parasternal long axis view just below the aortic valves by means of a Pulse-Doppler. All echocardiographic data were analyzed online and recorded on paper at 100 mm/s and on a commercially available analysis system (Sonowin®-2000, MESO). PWTh, EDD and ESD were corrected to body weight as rabbits on an atherogenic diet gained ~20% less weight compared to rabbits on a normal chow.

Echocardiographic measurements were made by two experienced observers (H.R. and K.H.) in a blinded fashion.
In order to assess the reproducibility of the echocardiographic measurements, studies were repeated on separate days in six normal rabbits and analyzed in a blinded fashion. The reproducibility, which was calculated as the difference between two determinations divided by the mean of the two determinations and expressed as a percentage, was shown to be excellent. Indeed, the percent error for EDD, ESD, PWTh, FS and EDA were 6.6±3.8%, 8.6±5.8%, 12.4±6.9%, 5.7±4.2%, 10.7±7.4%.

Table 2
Echocardiographic data

<table>
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<tr>
<td>n</td>
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<tr>
<td>ESD/BW</td>
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<tr>
<td>FS (%)</td>
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<tr>
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<tr>
<td>EDA/BW</td>
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Echocardiographic and histomorphometric data in sham-operated rabbits and rabbits with myocardial infarction (MI) treated with placebo or simvastatin for 9 weeks. Rabbits were either on a normal or atherogenic diet. IS, infarct size; BW, body weight; LVW, left ventricular weight; RVW, right ventricular weight; EDD, end-diastolic dimension; ESD, end-systolic dimension; PWTh, posterior wall thickness end-diastolic; FS, fractional shortening; Vcf, velocity of circumferential fiber shortening; HR, heart rate; EDA, end-diastolic area; Data are expressed as mean ± SEM. *P<0.05 vs sham; †P<0.05 simvastatin treatment vs MI/placebo; ‡P<0.05 vs corresponding group on normal diet.

2.4. Open-chest determinations of left ventricular function

Nine weeks after surgery rabbits were weighed, anesthetized and ventilated as described above. A 3F micromanometer-tipped catheter (Millar Instruments) was inserted into the LV via the right carotid artery. A midsternotomy was performed and a flow-probe (Transonic) was placed around the aortic root to measure the aortic flow (AF). After a 15-minute recovery period LV systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), heart rate (HR) and AF were recorded. The rates of maximum positive and negative left ventricular pressure development (dP/dtmax and dP/dtmin) were determined. The parameters were digitized for 10 cardiac cycles; averaged data are reported.

After haemodynamic measurements, a blood sample was taken from the auricular artery for determination of the CRP levels. Subsequently, the heart was quickly removed and...
weighed. LV and RV were separated and weighed. To confirm an equal distribution of MI sizes among the infarcted groups, infarct size was determined by planimetric analysis and expressed as percentage of the whole LV.

2.5. Plasma concentration of CRP

The CRP levels were determined with a commercial available ELISA (American Diagnostica Inc., USA).

2.6. Lipid levels

At the time of the echocardiography, a blood sample was taken from the auricular artery for determination of the lipid profile. Total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglyceride levels were directly measured with a commercially available enzymatic in vitro test (Roche Diagnostics) on automated clinical chemistry analyzer (Roche Diagnostics).

2.7. Rac1 GST-PAK pull-down assay

A glutathione-S-transferase (GST)-PAK-CD (PAK-CRIB domain) fusion protein, containing the Rac1 binding region from human PAK1B, was used to determine Rac1 activity as described [9]. Escherichia coli transformed with the GST-PAK-CD construct were grown at 37 °C to an absorbance of 0.3. Expression of recombinant protein was induced by addition of 0.1 mmol/L isopropylthiogalactoside for 2 h.

LV myocardium was homogenized and resuspended in lysis buffer (in mmol/L, Tris–HCl 50 [pH 7.4], NaCl 100, MgCl₂ 2, and benzamidine 1; NP-40 1%; glycerol 10%; leupeptin, pepstatin, and aprotinin 1 μg/mL) and centrifuged at 21,000 rpm for 5 min at 4 °C. Equal amounts of supernatant protein were incubated with the GST-PAK-CD fusion protein bound to glutathione-coupled sepharose beads at 4 °C for 30 min. Beads were washed 3 times with lysis buffer, eluted in Laemmli buffer (60 mmol/L Tris [pH 6.8], 2% sodium dodecysulfate, 10% glycerin, 0.1% bromphenol blue) and analyzed for bound Rac1 by Western blotting.

Fig. 1. (A) Left ventricular systolic pressure (LSVP) and (B) dP/dt max, parameter of systolic function, in sham-operated rabbits and rabbits with myocardial infarction (MI) treated with placebo (C) or simvastatin (Simva) for 9 weeks. Rabbits were either on a normal or atherogenic diet. Data are expressed as mean±SEM. n=7–8. * P<0.05 vs sham; † P<0.05 simvastatin treatment vs MI/placebo; ‡ P<0.05 vs corresponding group on normal diet.

Fig. 2. (A) Left ventricular end-diastolic pressure (LVEDP) and (B) dP/dt min, parameter of diastolic function, in sham-operated rabbits and rabbits with myocardial infarction (MI) treated with placebo (C) or simvastatin (Simva) for 9 weeks. Rabbits were either on a normal or atherogenic diet. Data are expressed as mean±SEM. n=7–8. * P<0.05 vs sham; † P<0.05 simvastatin treatment vs MI/placebo; ‡ P<0.05 vs corresponding group on normal diet.
2.8. Western blot analysis

The LV samples (non-infarcted LV myocardium) were homogenized in ice-cold RIPA buffer (150 mmol/L NaCl, 50 mmol/L Tris-Cl, 5 mmol/L EDTA, 1%v/v Nonidet P-40, 0.5%w/v deoxycholate, 10 mmol/L NaF, 10 mmol/L sodium pyrophosphate, 100 mmol/L phenylmethylsulfonyl fluoride, 2 μg/mL aprotinin, and 2 μg/mL leupeptin). Proteins were determined by Bradford assay. Myocardial extracts (30 μg protein per lane) were mixed with sample loading buffer (B7703, BioLabs) and separated on 12% SDS-polyacrylamide gel. Proteins were transferred onto PVDF membrane (Immun-Blot® 0.2 μm, Bio-Rad). The bands were detected using chemiluminescence assay (ECL +Plus, Amersham). Primary antibodies used recognize: SERCA2 ATPase (MA3-919, Affinity BioReagents); eNOS (N-30020, Transduction Laboratories), phosphorylated eNOS at Ser1177 (9571, Cell Signaling Technology) and glyceraldehyde-3-phosphate-dehydrogenase (GAPDH; Ab8245, Abcam).

2.9. Statistical analysis

Values are given as mean±SEM. Comparisons among mean values were made by factorial analysis of variance (ANOVA) followed by pair wise multiple comparisons using t test (two-sided) with Bonferroni adjustment, if appropriate. Lipid data were log transformed in order to achieve variance homogeneity before statistical analysis. A value of \( P<0.05 \) was considered statistically significant. All statistical analyses were performed with SigmaStat 2.03.

3. Results

3.1. Lipid profiles

The serum lipid profiles of the different groups are shown in Table 1. The atherogenic diet markedly increased serum levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Simvastatin significantly reduced all lipid parameters, however, total and LDL cholesterol remained markedly elevated in MI rabbits on the atherogenic diet (Table 1).

3.2. Infarct size, mortality, heart and body weights

In thirty five rabbits MI was induced by the ligation of a major branch of the LCx. Twenty one MI rabbits (60%) developed ischemia-induced ventricular fibrillation. Seventeen animals were successfully defibrillated, 4 animals died. The survival rate for the remaining study period of all MI rabbits was 100%. Infarct size was similar among the groups (Table 2).

Body weights were significantly lower in all groups on the atherogenic diet compared to the normal diet. LV weight/body weight ratio was increased in placebo-treated MI rabbits on the normal diet, but not significantly increased in MI rabbits on the atherogenic diet. Simvastatin slightly reduced the LV weights in both groups, although this did not reach statistical significance. In both simvastatin-treated MI groups, LV weight/body weight was not different from that of sham-operated animals (Table 2).

RV weight/body weight ratio increased in both normocholesterolemic and hypercholesterolemic MI rabbits compared to sham animals. Simvastatin treatment did not significantly affect RV weight/body weight ratio (Table 2).

3.3. Echocardiography and hemodynamics in animals on normal diet

Echocardiographic measurements were performed at baseline as well as 3 and 8 weeks after surgery (Table 2). In the placebo-treated group, MI resulted in a progressive increase in LV diameter which was slightly but not significantly reduced by simvastatin. LV function in the MI placebo group showed a progressive and significant impairment after MI as indicated by a decrease in FS and Vcf that was prevented by treatment with simvastatin (Table 2).

In the placebo-treated MI group on the normal diet, LVSP, \( \text{dP/dt}_{\text{max}} \), an index of myocardial contractility, and \( \text{dP/dt}_{\text{min}} \), an index of myocardial relaxation, were significantly reduced compared to sham-operated animals. LVEDP, on the other hand, was elevated (Figs. 1 and 2). Simvastatin treatment significantly improved LVSP, \( \text{dP/dt}_{\text{max}} \), and \( \text{dP/dt}_{\text{min}} \).

3.4. Echocardiography and hemodynamics in animals on atherogenic diet

In sham-operated rabbits, hypercholesterolemia did not significantly affect the echocardiographic or hemodynamic results.

![Fig. 3. Ratio of sarcoplasmatic-reticulum calcium (SERCA2) ATPase and of glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) protein expression in the left ventricle of sham-operated rabbits and rabbits with myocardial infarction (MI) treated with placebo (C) or simvastatin (Simva) for 9 weeks. Rabbits were either on a normal or atherogenic diet. Data are expressed as mean±SEM. \( n=7–8 \). * \( P<0.05 \) vs sham; † \( P<0.05 \) vs corresponding group on normal diet.](https://academic.oup.com/cardiovascres/article-abstract/72/3/438/327177?download=true)
In the placebo-treated rabbits on the atherogenic diet, MI resulted in a progressive increase in LV diameter that tended to be reduced by simvastatin. LV function showed a progressive and significant impairment in the MI placebo group that was prevented by treatment with simvastatin (Table 2). LVSP, dP/dt max, and dP/dt min were significantly more depressed after MI in placebo-treated rabbits on atherogenic diet than in normocholesterolemic animals (Figs. 1 and 2). Simvastatin treatment in hypercholesterolemic MI rabbits markedly improved LV function, which was not different compared to simvastatin-treated MI rabbits on a normal diet (Figs. 1 and 2).

3.5. SERCA-2 and eNOS expression, Rac1-PAK activity, and CRP levels in animals on normal diet

In all three groups receiving a normal diet, LV SERCA-2 protein expression and the phosphorylation of eNOS on Ser1177 were similar (Figs. 3 and 4). LV Rac1-GTPase activity and CRP levels were significantly increased after MI (Figs. 3 and 4). LV Rac1-GTPase activity and CRP levels were significantly increased after MI (Figs. 4B and 5), and normalized by simvastatin treatment.

3.6. SERCA-2 and eNOS expression, Rac1-PAK activity, and CRP levels in animals on atherogenic diet

In hypercholesterolemic MI rabbits receiving placebo therapy, LV SERCA-2 expression and eNOS phosphorylation were significantly reduced compared to the sham-operated group. (Figs. 3 and 4A). Simvastatin treatment prevented these changes.

Rac1-GTPase activity and CRP levels were markedly elevated in sham-operated animals on atherogenic diet compared to normocholesterolemic rabbits, but did not further increase after MI (Figs. 4B and 5). Simvastatin abrogated the increase in Rac1-GTPase activity and CRP levels in hypercholesterolemic MI rabbits.

4. Discussion

HMG CoA reductase inhibition improves the reduced left ventricular systolic and diastolic function in normocholesterolemic rabbits post-MI. Prolonged hypercholesterolemia in vivo induced by an atherogenic diet further impairs the depressed LV function after MI. Although simvastatin treatment only partially attenuated the elevation in cholesterol levels in these animals, LV function was normalized. Our data suggest that anti-inflammatory and anti-oxidative effects of HMG CoA reductase inhibition substantially contribute to the beneficial effects of this class of compound on cardiac function after MI.

Hypercholesterolemia is one of the major underlying risk factors of coronary artery disease [6,26] but there is only limited information regarding its direct effect on cardiac function and prognosis in animals and patients with heart failure [27,28] despite the fact that higher cholesterol levels...
have been associated with reduced mortality in patients with congestive heart failure [29]. On the other hand, while randomized studies are still lacking, recent investigations suggest that statins may reduce mortality in heart failure [30].

Albeit seeming paradoxically at first glance, potential explanations for these discrepant results exist and low cholesterol in the absence of heart failure and normal to elevated cholesterol levels may exert anti-inflammatory effects that are, at least in part, independent of lipid lowering. In general, while awaiting the results from randomized studies, patients with heart failure receive statin treatment to achieve target cholesterol levels, although no firm recommendations exist.

The cholesterol-fed rabbit represents one of the most important animal models for the study of atherosclerosis [19]. Additionally, several studies have shown that MI in rabbits results in LV remodeling and is associated with a significant impairment of systolic and diastolic LV function. While ischemia/reperfusion injury in isolated rabbit hearts was aggravated by prior hypercholesterolemia [31], no data are available after permanent coronary ligation as performed in the present study. We found that hypercholesterolemia further impairs the depressed LV function in rabbits post-MI. As similar infarct sizes were observed in all MI groups, differences in cardiac damage after coronary ligation are unlikely to underlie the results obtained. However, we identified several potential mechanisms by which hypercholesterolemia may aggravate, while statin treatment may improve, LV function.

In LV myocytes isolated from cholesterol fed rabbits, in vitro systolic and diastolic function was reduced. In parallel, SERCA-2 mRNA and protein expression as well as SERCA-2 mediated Ca²⁺-uptake activity were attenuated [3]. Abnormal Ca²⁺ handling by SERCA-2 plays a central role of in the pathophysiology of heart failure [32], and SERCA-2 gene transfer into failing rat hearts improved cardiac function and survival [33]. In our study, SERCA-2 expression was neither altered in sham-operated animals on an atherogenic diet nor in normocholesterolemic rabbits with MI. However, hypercholesterolemia caused a significant decrease in SERCA-2 protein expression in LV myocardial tissue from rabbits after MI. Simvastatin corrected the downregulation of SERCA-2 protein expression in hypercholesterolemic rabbits with MI which is likely to contribute to its beneficial effect on LV function.

Hypercholesterolemia in patients with coronary artery disease is associated with elevated plasma levels of pro-inflammatory cytokines as well as CRP, an independent predictor of cardiovascular endpoints such as MI and stroke [11]. Moreover, pro-inflammatory cytokines such as TNFα and CRP are also elevated in patients with heart failure and correlate with the severity and progression of the disease [34,35]. In rats, simvastatin reduced inflammation and improved LV remodeling after MI, although the impact of hypercholesterolemia was not investigated [36]. In our study, elevated plasma CRP levels in rabbits with chronic MI were further increased by the atherogenic diet suggesting that chronic inflammation contributed to the deleterious effect of hypercholesterolemia on LV function after MI. Simvastatin normalized plasma CRP in hypercholesterolemic rabbits with MI although it only partially attenuated the elevation of serum cholesterol levels. This apparent anti-inflammatory effect may explain why simvastatin not only prevented the deleterious effects of hypercholesterolemia but even ameliorated depressed LV function to a normal level observed in sham-operated animals. Indeed, data from recent large clinical trials in patients with acute coronary syndrome suggest that the early benefit of intensive statin treatment reflects anti-inflammatory actions of the drugs, particularly evident by a reduction in CRP [37].

Hypercholesterolemia in patients with coronary artery disease is characterized by an imbalance between NO and ROS resulting in reduced bioavailability of NO [10,38]. Increased ROS formation also contributes to the progression of heart failure [9,10,39,40], as indicated by attenuation of LV dilation and contractile impairment by the ROS scavenger dimethylthiourea in mice post-MI [41]. An important source of myocardial ROS formation is considered to be the NADPH oxidase [10], whose activity is regulated by the small GTP-binding protein Rac1. In failing human myocardium, NADPH oxidase-mediated ROS release is upregulated associated with increased Rac1 activity [9]. In the present study, MI in normocholesterolemic rabbits significantly increased the activity of Rac1. However, hypercholesterolemia was associated with a further increase in Rac1 GTPase activity together with a markedly decreased eNOS phosphorylation pointing to an imbalance between NO and ROS formation. Simvastatin prevented the increase in Rac1 activity and the attenuation of eNOS phosphorylation in hypercholesterolemic MI rabbits suggesting that a shift in the balance of NO and ROS contributed to the improvement of LV function [10]. The pivotal role eNOS for LV remodeling and function after MI was recently demonstrated in eNOS deficient mice that exhibited excess LV dysfunction, hypertrophy, and dilation [42]. The dual effect on NO and ROS formation may be one important mechanistic explanation for the effective amelioration of depressed LV function in MI rabbits by simvastatin treatment observed in the present study. Lipid-independent but eNOS-dependent pathways also contribute to the decreased brain infarct size in a mouse model of ischemic stroke and the limitation of myocardial remodeling by HMG CoA reductase inhibition [43,44].

In the present study, simvastatin slightly, albeit not significantly, reduced LV end-diastolic and end-systolic diameter assessed by echocardiography pointing to a reduction in LV enlargement as observed previously using cerivastatin in rats with heart failure induced by large MI [17,45]. The statin did not significantly affect LV and RV
hypertrophy that is part of the remodeling process seen in post-MI animal models. However, as the increases in LV weight after MI were only small, a large effect of HMG-CoA reductase inhibition may not be expected.

5. Conclusion

In summary, we have shown that hypercholesterolemia in vivo further impairs the depressed LV systolic and diastolic function in rabbits post-MI. Statin treatment effectively preserved LV function in normocholesterolemic as well as hypercholesterolemic animals, although the elevation of cholesterol levels in response to the atherogenic diet was only partially attenuated. Our study suggests that anti-inflammatory and anti-oxidative activities of simvastatin substantially contribute to its beneficial effects on cardiac function after MI.

References


