Published in final edited form as:

Semin Vasc Med. 2004 November ; 4(4): 377–384. doi:10.1055/s-2004-869594.

Statins and the Myocardium

Seema Mital, M.D.¹ and James K. Liao, M.D.²

¹*Division of Pediatric Cardiology, Columbia University, College of Physicians and Surgeons, New York, New York*

²*Vascular Medicine Research, Brigham & Women's Hospital, Harvard Medical School, Cambridge, Massachusetts*

Abstract

Cardiac hypertrophy and heart failure are leading causes of morbidity and mortality worldwide. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, have been shown to inhibit cardiac hypertrophy and improve symptoms of heart failure by cholesterol-independent mechanisms. Statins block the isoprenylation and function of members of the Rho GTPase family, such as Rac1 and RhoA. Because Rac1 is a requisite component of NADPH oxidase, which is a major source of reactive oxygen species in cardiovascular cells, the ability of statins to inhibit Rac1-mediated oxidative stress contributes importantly to their inhibitory effects on cardiac hypertrophy. Furthermore, inhibition of RhoA by statins leads to the activation of protein kinase B/Akt and upregulation of Type 3 nitric oxide synthase in the endothelium and the heart. This activation and upregulation results in increased angiogenesis and myocardial perfusion, decreased myocardial apoptosis, and improvement in endothelial and cardiac function. Because these effects of statins occur independent of cholesterol lowering, statins may have therapeutic benefits in nonhyperlipidemic patients with cardiac hypertrophy and heart failure.

Keywords

Cardiac hypertrophy; heart failure; G-proteins; protein kinase Akt; nitric oxide

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or “statins” are agents that inhibit the rate-limiting enzyme of cholesterol synthesis in the liver, thereby decreasing the hepatic production of cholesterol, increasing the expression of low-density lipoprotein receptors, and lowering the circulating levels of low-density lipoprotein cholesterol. Although it is widely accepted that the majority of clinical benefit obtained with statins is a direct result of their lipid-lowering properties, these agents appear to display additional cholesterol-independent or “pleiotropic” effects on various aspects of cardiovascular disease. These effects include improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response in the vascular wall.^{1–4} In normocholesterolemic animals, statin therapy has been shown to protect against stroke,⁵ ischemia-reperfusion injury of the heart,⁶ and vascular

Address for correspondence and reprint requests: James K. Liao, M.D., Director, Vascular Medicine Research, Brigham & Women's Hospital, Associate Professor of Medicine, Harvard Medical School, 65 Landsdowne Street, Room 275, Cambridge, MA 02139. The Use of Statins in Atherosclerotic Cardiovascular Disease; Editor in Chief, Jan Jacques Michiels, M.D., Ph.D.; Guest Editor, Jean Davignon, O.C., M.D.

Educational Objectives: Upon completion of this article, the reader should be able to (1) appreciate that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or statins have been shown to inhibit the development of cardiac hypertrophy and improve symptoms of heart failure, independent of their cholesterol lowering; and (2) recognize statins block the isoprenylation and function of small GTP-binding proteins, such as Rac and Rho, which mediate cardiac hypertrophy and heart failure.

inflammatory responses^{7,8} through mechanisms mediated by an increase in endothelium-derived nitric oxide (NO) production.

Many of these cholesterol-independent effects of statins are mediated by their ability to block the synthesis of important isoprenoid intermediates, which serve as lipid attachments for a variety of intracellular signaling molecules. In particular, the inhibition of the small GTP-binding proteins Rho, Ras, and Rac, whose proper membrane localization and function are dependent on isoprenylation,^{9,10} may play an important role in mediating the biological effects of statins. Although the main effect of statin therapy in cardiovascular disease appears to be predominantly vascular, recent animal and human studies indicate that statins may also have direct beneficial effects on the myocardium. In particular, statins have been shown to attenuate cardiac hypertrophy^{11,12} and improve cardiac function and symptoms in patients with congestive heart failure,¹³ irrespective of serum cholesterol levels.

STATINS IN CARDIAC HYPERTROPHY

Cardiac hypertrophy is an adaptive response of the heart to pressure overload. The molecular response to pressure overload is complex and may include modulation of various intracellular signal pathways, such as activation of many protein kinases (mitogen-activated protein kinase [MAPK] and phosphatidylinositol 3 kinase), expression of cardiac fetal genes (atrial natriuretic factor [ANF] and myosin light chain), and increase of protein synthesis. Furthermore, pressure overload leads to the release of secretion and the production of vasoactive peptides, such as angiotensin II and endothelin 1, that play pivotal roles in the induction of these hypertrophic responses.^{14,15} Recent studies indicate that the hyper-trophic process is also mediated, in part, by an increase in myocardial oxidative stress.^{12,16}

In the myocardium, Ras, Rho, and Rac are involved in the hypertrophic response.^{17,18} Ras-mediated cardiac hypertrophy has been demonstrated both in vitro¹⁹ and in vivo.²⁰ Transgenic mice that overexpress RhoA in the heart develop loss of systolic function and dilated cardiomyopathy.²¹ However, the development of cardiomyopathy is a result of abnormal conduction abnormalities rather than a direct modification of myocardial architecture. This effect of RhoA was unanticipated, because previously, several in vitro studies implicated RhoA in the development of hypertrophy.²² Other studies using cultured cardiomyocytes revealed that the activation of Rac is required in phenylephrine-induced cardiomyocyte hypertrophy. In those studies, transfection of myocytes with a dominant-negative mutant of Rac1 completely inhibited the hypertrophic response to phenylephrine.¹⁶ In addition, transgenic mice that specifically expressed activated Rac1 in the myocardium showed severe cardiac hypertrophy and dilatation.²³

Inhibition of this enzyme by statins leads not only to the reduction of cholesterol biosynthesis in the liver but also to the reduction of the synthesis of several isoprenoid intermediates (Fig. 1). Members of Ras and Rho GTPase family are major substrates for posttranslational modification by isoprenylation.^{9,10} Ras translocation from the cytoplasm to the plasma membrane is dependent on farnesylation, whereas Rho translocation is dependent on geranylgeranylation.^{1,24} These studies demonstrate that statins inhibit the development of cardiac hypertrophy through inhibition of Ras and Rho isoprenylation, leading to the accumulation of inactive Ras and Rho in the cytoplasm.^{12,25} Indeed, we have recently shown that Rac1 is a key mediator in the hypertrophic response.¹² Overexpression of a dominant-negative mutant of Rac1 (N17Rac1), and to a lesser extent RhoA (N19RhoA), inhibited angiotensin II-induced ANF promoter activity. Cotreatment with statins further decreased ANF promoter activity in cells transfected with N19RhoA and N17Cdc42, but not those transfected with N17Rac1. Similarly, cotreatment with GGPP reversed the inhibitory effects

of statins, whereas GGPP could not reverse the inhibitory effect of N17Rac1 on ANF promoter activity.

Recent evidence indicates that reactive oxygen species may be involved in the process of cardiac hypertrophy.^{26,27} The NADPH oxidase is a major source of superoxide in cardiovascular cells.²⁸ In the cardiomyocytes, three of these five components, p40^{PHOX} (PHOX for phagocyte oxidase), p47^{PHOX}, and p67^{PHOX}, exist in the cytosol, forming a complex. The other two components, p22^{PHOX} and gp91^{PHOX}, are bound to the membranes. Various stimuli lead to the phosphorylation of the cytosolic components, and the entire cytosolic complex then migrates to the membrane. Importantly, not only the core subunits are required for activation, but also two low-molecular-weight guanine nucleotide-binding proteins, Rac and Rap. During activation, Rac binds guanosine triphosphate and migrates to the membrane with the core cytosolic complex. Therefore, Rac is critically involved in the activation of cardiovascular NADPH oxidase.

A potent stimulator of cardiac hypertrophy, angiotensin II, increases the activity of vascular oxidase through NADPH oxidase activation.^{28,29} Thrombin, platelet-derived growth factor, and tumor necrosis factor also stimulate NADPH oxidase-dependent superoxide production in vascular smooth muscle cells (SMCs).^{30–32} Recent studies of the gp91^{PHOX}-deficient mice demonstrated that angiotensin II treatment increased cardiac hypertrophy and collagen content in wild-type but not gp91^{PHOX}-deficient mice.³³ This evidence further supports the hypothesis that myocardial oxidative stress, and in particular NADPH oxidase, plays a crucial role in cardiac hypertrophy. From these reasons, it is likely that statins could inhibit cardiac hypertrophy through an antioxidant mechanism involving the inhibition of Rac1 geranylgeranylation. Indeed, statins inhibit angiotensin II-induced oxidative stress and cardiac hypertrophy in rodents.¹² This has been observed in clinical studies in which statins inhibit cardiac hypertrophy in humans with hypercholesterolemia.¹¹

STATINS IN HEART FAILURE

The molecular mechanisms of the beneficial effects of statins in heart failure are not completely understood. Heart failure occurs as a result of hemodynamic, metabolic, and neurohormonal abnormalities. Reduced endothelial function is a key pathophysiologic event in heart failure and contributes to the progression from compensated to decompensated heart failure.³⁴ Loss of endothelial function is characterized by downregulation of NO production and endothelial NO synthase (eNOS) gene expression.^{34–36} The lack of NO contributes to myocardial apoptosis or programmed cell death, a critical event in cardiac remodeling and progression of heart failure.³⁷ The generation of free radicals and higher oxidative stress can cause inactivation of NO in heart failure.³⁸ Statins have been shown to reverse several of the abnormalities seen in association with heart failure. Statins can improve endothelial function and NO production,^{1,24} inhibit the generation of oxygen free radicals,³⁹ and prevent myocyte apoptosis,⁴⁰ and they may also attenuate vascular inflammation through modulation of the Rho/Rho-kinase pathway.

Animals Studies

To determine the efficacy of statins in heart failure, we administered statins to healthy animals and to animals with heart failure.⁴⁰ Cardiac hemodynamics and cardiac NO production was measured at baseline and after 2 weeks of statin administration and was compared with controls. The administration of veratrine, a cholinergic NO-dependent vasodilator, and acetylcholine, an endothelium-dependent vasodilator, resulted in a greater increase in coronary blood flow in statin-treated animals compared with controls (Fig. 2a). eNOS enzyme expression measured by Western blots was higher in thoracic aortic endothelium of statin groups compared with controls. As a consequence, nitrite production in response to acetylcholine was higher in

isolated coronary microvessels from statin-treated canine hearts compared with untreated controls (Fig. 2b). The response to endothelium-independent vasodilators—adenosine and nitroglycerine—was not potentiated in the treated group. Basal myocardial oxygen consumption in the statin group was significantly lower than the control group (5.9 ± 0.4 vs 6.8 ± 0.6 mL/minute). This study showed the ability of statins to decrease myocardial oxygen consumption and increase myocardial oxygen reserve through increase in NO production.

To determine whether the ability of statin to increase cardiac NO production has beneficial effects in heart failure, we performed additional studies in a canine pacing model of heart failure.⁴¹ The time to the development of end-stage heart failure was longer in the statin group (34 days) compared with in the untreated group (29 days). Furthermore, statin-treated dogs had a lower left ventricular (LV) end-diastolic pressure at 4 weeks of pacing compared with the untreated group (18 ± 1 vs 25 ± 1 mm Hg). LV dp/dtmax, a measure of cardiac function, was also higher in the statin group at 4 weeks compared with in the untreated group. Endothelium-dependent coronary vasodilation was preserved in the treated group compared with controls. Myocardial eNOS expression was higher in the statin group compared with in the untreated group. These effects were independent of cholesterol lowering. The findings of this study indicate that statin treatment retards the progression of heart failure, which may be related to its ability to preserve endothelial function and cardiac NO production.

Recent studies have demonstrated a direct angiogenic effect of statins, with reports of neo-angiogenesis in ischemic limb vasculature following treatment with statins.⁴² We investigated whether statins promote angiogenesis in heart failure and prevent myocardial apoptosis in Syrian cardiomyopathic hamsters.⁴³ Interestingly, LV shortening fraction decreased from $17 \pm 1\%$ to $9 \pm 2\%$ in the untreated group but did not deteriorate in the statin group ($16 \pm 2\%$ at 6 weeks). Statin-treated animals had less LV dilatation compared with the untreated group (Fig. 3). Myocardial caspase 3 activity was higher and apoptotic nuclear density was lower in statin compared with in untreated cardiomyopathic hamsters ($0.072 \pm 0.02\%$ vs $0.107 \pm 0.03\%$). Myocardial capillary density estimated by percentage of eNOS-stained capillaries was higher in the statin group compared with the untreated groups, as well as compared with the healthy controls. This study demonstrated that the ability of statin to promote new blood vessel formation is not limited to peripheral ischemia but is also seen in heart failure. Indeed, the mechanism is probably in part a result of the activation of protein kinase Akt, which is stimulated by statins.⁴² The improvement in coronary perfusion may help compensate for the increased demands of a hypertrophied and dilated myocardium and prevent cardiomyocyte death. These findings indicate that systemic administration of a statin can mimic the effects of local gene transfection into failing hearts on new blood vessel formation and provides a novel mechanism for the benefit of statins in heart failure.

Finally, another mechanism by which statins may regulate the development of cardiomyopathy and heart failure is via effects on mitogen-activated protein kinases (MAPKs). MAPKs are a superfamily of protein kinases that regulate the transcription of genes that mediate cardiac growth and hypertrophy. The three major members of the family, extracellular signal-regulated kinase, c-jun N-terminal kinase (JNK), and p38-MAPK, phosphorylate other signaling proteins (notably transcription factors and other protein kinases) to regulate cell growth and survival.^{44,45} Studies using transgenic overexpression of MAPKs indicate that the activation of extracellular signal-regulated kinase may promote cell growth and survival, whereas the activation of JNK and p38 MAPK promotes the development of cardiac dilatation and dysfunction.⁴⁵ Inhibiting p38 MAPK can reduce cardiac hypertrophy and dysfunction.⁴⁶ Dechend et al have previously shown that statin can ameliorate angiotensin II-induced cardiac hypertrophy and remodeling independent of cholesterol-lowering.²⁵

To determine whether alteration of MAPK signaling by statins could contribute to their beneficial effects in heart failure, we studied the effect of statin administration in mice with targeted disruption of the bradykinin 2 receptor. These mice develop LV hypertrophy that progresses to a dilated cardiomyopathy and overt heart failure over a 12-month period, which may be related, in part, to reduced NO availability. Statin treatment decreased LV mass, volume, and mass/volume ratio and improved LV shortening fraction in bradykinin 2 receptor mice compared with wild-type mice. These effects were blocked by concomitant treatment with the NO synthase inhibitor L-NAME, indicating that the beneficial effects of statins are mediated in part by increased NO. Furthermore, KO mice had higher expression of JNK and p38 MAPK compared with wild-type mice. Statin treatment was associated with decreased activation of JNK and p38 MAPK in KO mice but had no effect on extracellular signal-regulated kinase activation. Because eNOS activation is also regulated by MAPKs, the ability of statin to upregulate eNOS mRNA may be related to altered MAPK activation.⁴⁷ The ability to decrease the activation of JNK and p38 MAPK provides an additional mechanism by which statin can prevent progressive cardiac remodeling and exert beneficial effects in heart failure.

Clinical Trials

In a recent prospective, double blind, placebo-controlled study, 51 patients with symptomatic, nonischemic, dilated cardiomyopathy were randomly divided into two groups receiving statin ($n = 24$) or placebo ($n = 39$) for 14 weeks.¹³ Although patients receiving statins exhibited a modest reduction in serum cholesterol level compared with patients receiving placebo (130 ± 13 mg/dL vs 147 ± 14 mg/dL, respectively), these patients demonstrated a remarkable improvement in exercise endurance as exhibited by a lower New York Heart Association functional class, compared with patients receiving placebo (2.04 ± 0.06 vs 2.39 ± 0.07 , $p < 0.01$). This advance corresponded to improved left ventricular ejection fraction in the statin group (from $33 \pm 4\%$ to $41 \pm 4\%$, $p < 0.01$), but not in the placebo group. The improvements in the exercise endurance and heart function of the statin group was in addition to the improvements already observed with two current treatments for heart failure, β -blockers and ACE inhibitors. Furthermore, plasma concentrations of tumor necrosis factor α , interleukin 6, and brain natriuretic peptide were lower in the statin group compared with in the placebo group. This study indicates that short-term statin therapy improves cardiac function, neurohormonal imbalance, and symptoms associated with idiopathic dilated cardiomyopathy and also indicates that statins may have therapeutic benefits in patients with heart failure, irrespective of serum cholesterol levels or atherosclerotic heart disease.

CLINICAL IMPLICATIONS

Strong experimental evidence and some recent clinical studies indicate that statins can prevent cardiac hypertrophy, irrespective of serum cholesterol levels. This effect is most likely mediated by inhibition of Rac1 isoprenylation and includes a reduction in myocardial oxidative stress, indicating a novel pharmacological approach to treating cardiac hypertrophy. However, caution should always be exercised when attempting to extrapolate results obtained from animal studies to the clinical setting. Thus, further studies in nonhyperlipidemic patients with cardiac hypertrophy are warranted, using statin therapy to determine whether or not these effects are truly cholesterol independent. Similarly, statins reduce the incidence of heart failure in patients with coronary artery disease.^{48,49} However, this may be in large part caused by a reduction in recurrent coronary events via cholesterol reduction and subsequent beneficial effects on LV remodeling. Nevertheless, our findings that short-term statin therapy improves cardiac function should pave the way for further large-scale clinical trials to evaluate the long-term clinical benefits of statin therapy in normocholesterolemic patients with nonischemic, dilated cardiomyopathy.

ACKNOWLEDGEMENTS

This work described in this article was supported by the National Institutes of Health (HL-52233, HL-48743, to Dr Liao), the American Heart Association Bugher Foundation Award (to Dr Liao), and the American Heart Association, Heritage Affiliate, Scientist Development Grant (to Dr Mital).

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Figure 1.

Cholesterol biosynthesis. HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A. HMG-CoA reductase is a rate-limiting enzyme, and this blockade (statins) leads to the reduction of other isoprenoid intermediates such as mevalonate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate, as well as intracellular cholesterol.

Figure 2. Effect of statins in HF. The line graph shows serial changes in left ventricular (LV) shortening fraction in (A) untreated heart failure and (B) statin-treated cardiomyopathic hamsters. * $p<0.05$ from baseline; ‡ $p<0.01$ from HF. HF, heart failure; Ham, hamster.

Figure 3.

Effect of statins on angiogenesis and eNOS. (A) Left ventricular myocardial capillary density (i.e., the number of capillaries per three high-power fields) in the statom-treated cardiomyopathic hamsters (open bar) compared with controls (solid bar) and untreated cardiomyopathic hamsters (hatched bar) ($n = 6$ in each group). $^{\dagger}p < 0.01$ from controls; $^{\ddagger}p < 0.01$ from untreated HF hamsters. (B) Representative microscopic images of myocardial sections stained for eNOS in the three groups of hamsters are shown. The brown staining (red arrows) represents eNOS staining of capillaries. HF, heart failure; Sim, simvastatin; eNOS, endothelial nitric oxide synthase.